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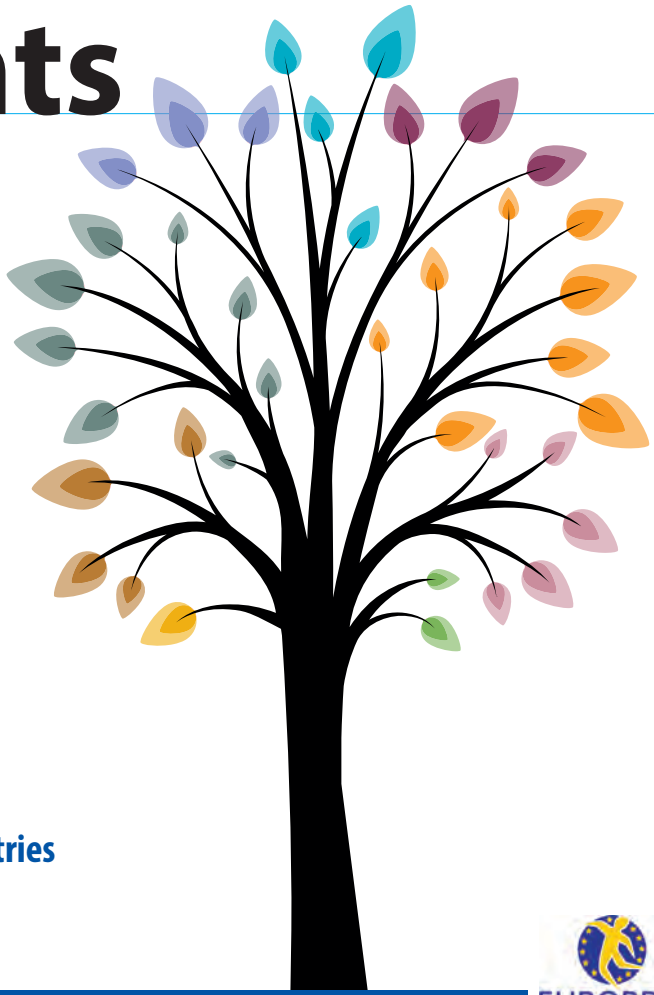
The **Voice** of Rare Disease **Patients**



Experiences and Expectations of over 3,000 Patients on Rare Disease Patient Registries in Europe

EURORDIS
Rare Diseases Europe

The **Voice** of Rare Disease **Patients**

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A report based on
the EPIRARE project

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FOREWORD

Citizen's health is a top priority for the European Commission. Investing in health is about making the most of human capital and about driving for innovation and economic growth.

The Directorate General for Health and Consumers and the Joint Research Centre of the European Commission congratulate EURORDIS for its continuous effort in giving a voice to the 30 million people affected by rare diseases throughout Europe. The EPIRARE (European Platform for Rare Disease Registries) project report presenting patients' experiences and expectations is an essential and timely contribution to address some specific challenges we are facing in rare disease healthcare and research. With this publication, rare disease patients make it clear that it is fundamental to have access to adequate, standardised information about all the aspects of rare diseases, from natural history to diagnosis and from treatment to quality of life of patients and their families. The participants to this survey show an overwhelming support for the creation of a common European infrastructure supporting registries.

The Commission services fully agree with patients' organisations and healthcare professionals that disease registries are "an indispensable infrastructure tool for translating basic and clinical research into improved care and therapeutic solutions".

Following the example in other areas, where the Directorate General for Health and Consumers and the Joint Research Centre are successfully cooperating with each other, these services have agreed to join competences and to develop together with patient groups and with member states' experts the European Platform on Rare Diseases Registration. The European Commission services thus decided to pool their competence.

In order to avoid fragmentation, inconsistency, lack of common standards and absence of interoperability a corporative approach is required across the EU and we need to pool knowledge and to invest in coordination, cooperation and commitment.

We are looking forward, together with you, to implement the proposed policy scenarios for a European Platform for Rare Disease Registries and to contribute to the well-being of this large group of patients. This report will be an invaluable guidance to accomplish this challenging task.

Paola Testori Coggi
Director-General
Directorate General for Health and Consumers
European Commission

Dominique Ristori
Director-General
Joint Research Centre
European Commission

PREFACE

The publication of this book comes at a moment when the European landscape on patient registries is undergoing a profound and progressive convergence of efforts. This new wave of participation in rare disease patient registration is leading to a strategic breach in longstanding barriers that have plagued effective collection and sharing of data necessary to underpin rare disease research and the development of safe and effective treatments, ultimately culminating in a collective health gain for people living with rare diseases.

This book also represents a new era in patient data collection where patients have raised the bar in terms of the quality and scope of their involvement. More and more patients now take an active role in initiating, designing, funding, and even directly collecting and sharing data within their own registry. As patients' empowerment steadily grows alongside their acute, disease-specific knowledge, they are able to reflect meaningfully on the issues surrounding patient registration, and illuminate the path forward.

Through an extensive consultation rare disease patients in Europe through its membership, EURORDIS has been successful in keeping a finger on the pulse of patient experiences, and expectations of rare disease patient registries during the last decade. The patient voice is now able to drive innovation in patient registration solutions in collaboration with all stakeholders. The collection of survey data, from which the contents of this book are derived, was conducted by EURORDIS as part of the EPIRARE project. Over the three-year course of the project, EURORDIS was responsible for proposing policy scenarios for rare disease patient registration based on the survey results and the consensus built amongst all stakeholders. The proposed scenario describes the development of an EU Platform for rare disease patient registration and data collection - an optimal public health tool bringing high added-value for the Community and creating value for all interested parties, while serving public interest.

Co-funded by the European Commission within the EU Program of Community Action in the field of Public Health, Genzyme, Novartis, and Millennium Pharmaceuticals: The Takeda Oncology Company and coordinated by the Istituto Superiore di Sanità at the Italian Ministry of Health, the project has prepared the ground for the creation of an EU platform for the collection of rare disease patient data.

EURORDIS continues to hold patient registries as an advocacy priority and is actively participating in the current major EU projects in the field, such as RD Connect and the EUCERD Joint Action: Working for Rare Diseases, which are shaping and implementing an EU strategy on registries that will be coordinated and patient-centred. It is a great opportunity to consider specific patient expectations alongside all other stakeholders as European and global solutions in rare disease patient registries are proposed. Although rare disease patient registries are most often managed by universities, industry or public administrations, they ultimately belong to the patients. Therefore, it is crucial and necessary to involve them actively in this process.

Yann le Cam
Chief Executive Officer
EURORDIS

In April of 2011, EURORDIS embarked with 11 project partners on the EPIRARE project, aimed at building consensus and synergies for the EU registration of rare disease patients. The project was co-funded by the European Commission within the EU Program of Community Action in the field of Public Health and coordinated by the Italian National Centre for Rare Diseases of the Istituto Superiore di Sanità in Rome, Italy.

Within this latter objective, the project has prepared the ground for the possible future creation of an EU platform, which supports the registration of rare disease patients by promoting the standardization of procedures, the quality of data collection, facilitating data comparability and providing common services to facilitate the collection of data and to improve the use of registries for different purposes. It is expected that a common reference framework, addressing scope, governance and long-term sustainability at the EU level, will avoid wasteful fragmentation and duplication of time and resources, and facilitate the setting up of more patient registries, especially for the rarest and most fragmented diseases throughout Europe.

In order to devise a platform, which could successfully draw the interest of stakeholders and become an attractive resource for new and existing registries, a number of consultations were planned. The first step included a survey of existing rare disease patient registries (EPIRARE Registry Survey) to characterize their operation conditions and identify their needs. The survey addressed specific characteristics of existing registries, such as scope and aims, legal basis for collection of data, measures for data protection, organisational and financial support, number of patients registered, unmet needs, data collected, means of collection, data sources and quality of data, as well as ethical standards. The EPIRARE Registry Survey targeted the largest possible number of research, academic and industry registries to understand the state of the art from the perspective of registry holders. A parallel EPIRARE Patient Survey was conducted by EURORDIS in order to specifically identify patient registry initiatives and collect the experience and expectations of patient organisations in this field. The analysis that follows in this publication includes the results of the EPIRARE Patient Survey and major trends observed in the experience and expectations of patients and their representatives in RDPR. Some comparisons of these results with those of the EPIRARE Registry Survey were also made. Finally an analysis of differences in opinions between countries, diseases and additional characteristics of the disease (age of onset, prevalence and genetic nature) was also conducted.

As one of the major partners in the EPIRARE project involved in the survey and most other project activities, EURORDIS was well prepared to tackle the task of defining possible policy scenarios on the scope, common data set, governance and sustainability of rare disease patient registration described in the discussion and conclusions of this text. This essential prerequisite to define national, European and international strategy and concrete actions on patient registries will provide the European Commission with robust elements and consensus amongst stakeholders to define the future policy for the EU registration of rare disease patients.

Domenica Taruscio
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Patient registries for rare diseases (RD) were long regarded as research tools for epidemiologists, and did not capture the imagination of scientists, industry, policy makers and patients. This perception has dramatically changed over the last decade for two major reasons – the advances in information and computer technology, and the advances in RD research. RD patients benefit from "fit-for purpose" registries in many ways, as registration addresses one of the key problems in RD, pulling information together from geographically and structurally dispersed sources, and making this information available for research and health care purposes. EURORDIS has actively contributed to several exemplar European Commission-funded projects (such as TREAT-NMD, EPIRARE and RD-Connect) in developing and utilizing RD registries to maximize the benefits for patients. Similar principles apply to RD biobanks (such as EuroBioBank) where the same type of information is associated with precious, sometimes unique samples that patients donated for research. Progress has not only been made in the science, but also in the safe and ethical conduct of patient registration, with widely recognized guidelines available from the European Union Committee of Experts on Rare Diseases (EUCERD) and the International Rare Diseases Research Consortium (IRDiRC). Moreover, involvement of patients and patient organizations in research and registries not as "objects", but as active participants, ambassadors and governors has been a key achievement for RD patient registries. The genomic revolution will offer additional opportunities for improving health for patients with RD through advancing research, and integrating data from –omics research with phenotypic information (patient registries) and biomaterials (biobanks) is the key aim of RD-Connect, an EU funded project under framework programme 7 from 2012-2017.

While patient registries are a core part of ongoing and future research in RD, their ability to capture a largely unrecognised public health need is also of increasing concern. For RD patients to be visible to their health care systems, reliable data collection that fulfils public health purposes is required. Recognising the multiple registries that are now in existence for RD and the various roles that they play, the EUCERD produced recommendations for RD registries and data collection, stressing the need for their interoperability and the use of common coding protocols. The European Commission is responding by developing a feasibility analysis of a RD registries platform utilising the Joint Research Centre. As data collection on RD patients is highlighted as an integral part of the national planning process for RD, as well as forming a key component of future European Reference Networks, the future of RD registries should be secured.

The patient registry survey carried out by EURORDIS is a crucial contribution to the overall findings of the EPIRARE project and its conclusions for the future. It is based on an unprecedented amount of information gathered from patient organizations. It adds valuable information and provides new insights into patients' expectations which need to be at the forefront of our planning for RD registries in the future, both in addressing the needs for research and for public health.

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EPIRARE SURVEY TOTAL LIST OF DISEASES COVERED - Williams syndrome - Behcet disease – Scleroderma - Duchenne muscular dystrophy - Cystic fibrosis - Rett syndrome - Idiopathic achalasia - Familial spastic paraplegia - Idiopathic panuveitis - Neurofibromatosis type 1 - Ehlers-Danlos syndrome type 1 - Proximal spinal muscular atrophy - Tuberous sclerosis - Beta-thalassemia - Idiopathic steroid-sensitive nephrotic syndrome - Systemic lupus erythematosus - Prader-Willi syndrome - Myasthenia gravis - Epidermolytic epidermolysis bullosa - Hereditary angioedema - X-linked Charcot-Marie-Tooth disease - Dravet syndrome - MELAS syndrome - Fragile X syndrome – Lymphangioleiomyomatosis - Angelman syndrome - Crohn's disease - Arnold-Chiari malformation type II - Essential thrombocythemia - Friedreich ataxia – Phenylketonuria - Rendu-Osler-Weber disease - Barrett esophagus - Common variable immunodeficiency – Hemophilia - Wegener granulomatosis –Achondroplasia - Bladder exstrophy - Osteogenesis imperfecta – Epilepsy - 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INTRODUCTION

THE IMPORTANCE OF RARE DISEASE PATIENT REGISTRIES

Rare Disease Patient Registries (RDPR) represent a fundamental research effort upon which a number of critical activities are based. They constitute key instruments for increasing knowledge on rare diseases (RD) by pooling adequate thresholds of data for fundamental, clinical research, and epidemiological research. RDPR are vital to the assessment of the feasibility, planning and design of clinical trials and facilitate the enrolment of patients for real-life post-marketing observational studies. It has been demonstrated that RDPR are a major determinant for successful translational research in the field of RD. Where well-implemented registries and active patient organizations exist, the likelihood for developing a treatment for the disease in question is increased[1].

Furthermore, and of great importance for patients and families, the consistent longitudinal collection of patient data facilitates the creation of standards of care and dramatically improves patient outcomes and life expectancy even in the absence of new therapies. RDPR broadly support health and social service planning by playing a pivotal role in healthcare organisation. They represent a necessary infrastructure for the implementation of the European Reference Networks for RD.

These compelling arguments for RDPR as indispensable infrastructure tools for translating basic and clinical research into improved care and therapeutic solutions have elevated their status to a major priority for all stakeholders, making them a building block of any sound policy on RD at the national, European and international level.

OBSTACLES IN RARE DISEASE PATIENT REGISTRIES

It has widely been recognised that collaborative efforts in RDPR are paramount to establishing, managing and deriving meaningful outcomes in the most efficient manner and for the uppermost benefit to patients. A complete list of the existing 600 rare diseases registers in Europe can be found in the Orphanet Report - Disease Registries in Europe - January 2013.[2] Nevertheless, no uniform, accepted standards currently govern the collection, organisation or availability of data collected in RDPR.

Despite an increase in RD patient registration initiatives, variability, fragmentation and challenges to concert efforts in the registration of rare disease patients abound due to several major factors:

- Number of stakeholders and variability in stakeholder's needs and objectives
- Inconsistency in financial sustainability of registries
- Lack of common standards leading to variability in data collection and quality
- Lack of resources to maintain separate registries for each rare disease or each stakeholder objective

Specific features of rare diseases make the registration of patients living with them additionally challenging:

- Genetic nature of most RD implying the need to investigate and trace family related cases
- Scarcity of cases imposing a large geographical coverage of data collection requiring multiple collaborations and exchanges of data, usually transnationally
- Nearly equal cost of establishing and maintaining RDPR as compared to prevalent diseases yet a much greater difficulty to obtain funding for the latter

In addition, the landscape of rare disease patient registration is continually changing. At the time of this publication:

- The proposed General Data Protection Regulation[3] could possibly create important challenges to European-wide data collection and exchange.
- Some Member States (MS) are currently establishing RD data collections as part of national plans for RD at the national level with little cross talk with other initiatives. Other MS have no such plans for registries yet.
- Data collection is highlighted as a priority for future ERN[4] but the linkage of this process to European research infrastructures as well as national and other international data collections is not yet clear, and needs to be defined.
- Targeted data extraction from electronic health records (EHR) rather than separate data collection methodologies per se is likely to be the future vision of RD registries but is not yet operational[5].
- Research progress and sound study design in disease areas lacking adequate natural history data, acceptable biomarkers, and valid endpoints will continually require interoperability between research registries and other research infrastructures such as biobanks and genetic databases.
- Increased regulatory requirements for post-marketing surveillance for orphan medicinal products are foreseen and provide the possibility of public-private partnerships in some but by no means all RD areas.

The existence of these considerable barriers creates an undeniable argument for developing globally accepted definitions, classifications and data standards as well as favourable, congruent policies and resources for RDPR that sustainable over time.

CURRENT EUROPEAN UNION POLICY FRAMEWORK

The European Commission has long proposed in its Communication[6] "Rare Diseases: Europe's Challenges" that MS put in place strategies aimed at ensuring mechanisms to gather national data on RD and pool it together with European counterparts.

It further highlighted the importance for the development of research and healthcare infrastructures in the field of RD in the Council Recommendation on an Action in the Field of Rare Diseases[7] accompanying this communication. RDPR have been listed as such infrastructures and given their long-lasting nature, the need for appropriate financial provisions at the national level to ensure their sustainability is vital.

RDPR are one of the main pillars of the current EU policy framework on national plans for RD. The European Project for Rare Diseases National Plans Development (EUROPLAN) recommendations underscore the importance for MS to stimulate and support national initiatives in a European or international framework in the domain of registries and of their uses for research, epidemiology and clinical purposes, and for health and social services planning.

These policy recommendations have culminated in the European Commission's strategic objective to create a European Platform on Rare Diseases Registration (herein referred to as the Platform). This Platform is scheduled to be located in the Commission's science-based, decision-making Joint Research Centre (JRC) with the objective of providing common services and tools for the existing (and future) rare diseases registries in the European Union.

Seven major stakeholders in the European and international RD Community have been invited in an iterative stakeholder engagement process to expand on key issues surrounding the development, maintenance and sustainability of the Platform. Stakeholders include patient representatives, health care providers, funding agencies, government regulatory and public health agencies (national and European), researchers and industry.

During this consensus reaching process the foremost expectations from the major stakeholders groups regarding the evolution of the Platform and its foreseeable outputs are summarised as follows:

- Patients: see healthcare and social planning as an extremely important aim of the platform amongst others such as therapy development and monitoring, good clinical practices and research on care protocols and overall knowledge generation.
- Patient Organisations: recognise the value that the Platform will present in raising awareness in the medical, research, policy-making and public environments as well as helping structure provision of care.
- Healthcare providers: value the supportive role the Platform will play in overall knowledge development, improvements of good clinical practices and therapy development.
- Health Authorities: highlight the importance of the Platform in healthcare and social planning as well as evidence generation for therapy decision-making and intervention.
- Industry: recognises the Platform as a high quality source of data as well as a framework for public-private partnership.
- Registry holders: anticipate the Platform to allow optimization of the research tools and effective knowledge generation.

EURORDIS REFLECTION PROCESS

EURORDIS holds Patient Registries as an advocacy priority and began its reflection on this topic in 2006. The following project activities and stakeholder meetings have served as opportunities for EURORDIS to gather and communicate the experiences and expectations of the RD patient community on the subject of RDPR:

Nov 2006 > 5th EURORDIS Round Table of Companies (ERTC) Workshop, Paris. *"Rare Disease Patient Registries: an Essential Tool in the Development of Therapies?"*

Jan 2007 > EURORDIS joins as partner in the TREAT-NMD project whose focus is on the development of tools (including a global patient registry) that industry, clinicians and scientists need to bring novel therapeutic approaches for neuromuscular diseases

May 2008 > EURORDIS Membership Meeting, Copenhagen. *"Acting together for patient-centred care for rare diseases".*

Mar 2009 > EPPOSI Workshop, Brussels. *Patients' Registries For Rare Disorders Need for Data Collection to Increase Knowledge on Rare Disorders and Optimize Disease Management and Care.*

Mar 2009 > EURORDIS Membership Meeting, Athens. Workshop on Registries.

May 2010 > EURORDIS European Conference for Rare Diseases, Krakow. *Theme 3: Science from the bench to the bedside - Databases and Registries.*

Apr 2011 > EURORDIS joins EPIRARE (European Platform for Rare Disease Registries) project whose objectives include defining the state of the art, addressing the feasibility of an EU legal instrument for data sharing, agreeing on a common data elements, and proposing the aims, scope, governance and sustainability options for a European Platform for rare disease patient registries.

June 2011 > Rare Disease Task Force (RDTF) Workshop on Rare Disease Registries (update to 2008 Workshop report), Paris.

Oct 2011 > European Medicines Agency/ EUCERD Workshop, London: Towards a Public-Private Partnership for Registries in the Field of Rare Diseases.

Jan 2012 > EURORDIS – European Cancer Patient Coalition (ECPC) Joint Workshop on rare disease/cancer patient registries. A workshop in the European Parliament on the importance of patient registries for patients with rare cancers and rare diseases.

Oct 2012 > EPIRARE Rare disease and orphan drug registries International Workshop, Rome.

Nov 2012 > EUCERD Joint Action: Workshop Report on Rare Disease Registration, Luxemburg. Drafting group and breakout session discussions 29- 30th January 2013

Jan 2013 > EURORDIS joins RD Connect project whose major aim is developing an integrated research platform combining clinical patient profiles (registries) with sample availability (biobanks) and -omics data to facilitate rare disease research funded under IRDiRC.

Apr 2013 > Joint EPIRARE & EUCERD-Joint Action Workshop, Paris. Rare Disease data collection and European Registry Platform

May 2013 > EURORDIS Membership Meeting, Dubrovnik. Workshop 4, Rare Disease Patient Registries

2011-2014 > EUROPLAN: **39 Conferences and National Plans for RD in 20 Member States** and 4 additional European countries organised by EURORDIS, National Alliances for RD, national competent authorities and all stakeholders on six main policy areas including RDPR.

Following these reflections and in parallel with RD patient communities in the United States and Canada, EURORDIS released a **Joint Declaration of 10 Key Principles for Rare Disease Patient Registries** with the National Organization for Rare Disorders (NORD) and the Canadian Organization for Rare Disorders (CORD)[8]. These ten key points reflect the recognition by the patient community that RDPR constitute key instruments for advancing knowledge, research, care and treatment for RD. The topic of RDPR was appealing enough to enable this first-consensus into an international declaration by RD patient groups.

The key principles also underscore the importance that patient involvement holds in the successful establishment and long-term maintenance of RDPR and that many patient groups are already very active and capable in this role.

EURORDIS-NORD-CORD
Joint Declaration of10 Key Principles for Rare Disease Patient Registries

(SUMMARY)

1. Patient Registries should be recognised as a global priority in the field of Rare Diseases.
2. Rare Disease Patient Registries should encompass the widest geographic scope possible.
3. Rare Disease Patient Registries should be centred on a disease or group of diseases rather than a therapeutic intervention.
4. Interoperability and harmonization between Rare Disease Patient Registries should be consistently pursued.
5. A minimum set of Common Data Elements should be consistently used in all Rare Disease Patient Registries.
6. Rare Disease Patient Registries data should be linked with corresponding biobank data.
7. Rare Disease Patient Registries should include data directly reported by patients along with data reported by healthcare professionals
8. Public-Private Partnerships should be encouraged to ensure sustainability of Rare Disease Patient Registries.
9. Patients should be equally involved with other stakeholders in the governance of Rare Disease Patient Registries.
10. Rare Disease Patient Registries should serve as key instruments for building and empowering patient communities.

These common reflections and principles will serve as a reference to all other stakeholders when shaping policies and taking actions in the field of RDPR.

The EURORDIS-NORD-CORD declaration has already been considered, in part, as a basis for the EUCERD Core Recommendations on Rare Disease Patient Registration and Data Collection to the European Commission, Member States and All Stakeholders[9].

It is expected that in concert with the findings and conclusions of the EPIRARE Patient Survey on RDPR, these recommendations will help shape national and EU policies on rare disease patient registration. The EUCERD Recommendations will guide the strategy for the Platform and constitute the core guiding principles for its governance structure and technical aspects.

European Committee of Experts (EUCERD)
Core Recommendations on Rare Disease Patient Registration and Data Collection to the European Commission, Member States and All Stakeholders

(SUMMARY)

1. RD patient registries and data collections need to be internationally interoperable as much as possible and the procedures to collect data elements need to be harmonised and consistent, to allow pooling of data when it is necessary to reach sufficient statistically significant numbers for clinical research and public health purposes.
2. All sources of data should be considered as sources of information for RD registries and data collections, to speed up the acquisition of knowledge and the development of clinical research.
3. Collected data should be utilised for public health and research purposes.
4. Patient registries and data collections should adhere to good practice guidelines in the field.
5. Existing and future patient registries and data collections should be adapted to serve regulatory purposes, where required.
6. Patient registries and data collections should be sustainable for the foreseeable timespan of the registries' utility.

EPIRARE PROJECT

In April of 2011, EURORDIS was invited with 11 project partners to embark on the EPIRARE (European Platform for Rare Diseases Registries) project co-funded by the European Commission within the EU Program of Community Action in the field of Public Health and coordinated by the Istituto Superiore di Sanità (ISS) at the Italian Ministry of Health.

The project's major achievements include

- Analysis of the present situation by conducting a survey targeting existing registries and to identify good practices
- Building consensus and synergies to address the regulatory, ethical and technical issues associated with the registration of rare disease patients in Europe
- Elaboration of possible policy scenarios for EU policies on RDPR
- Preparation of the feasibility of a future EU rare disease registry platform

The project has prepared the ground for the possible future creation of an EU platform for the collection of data on RD patients. It is expected that a common reference framework, addressing scope, governance and long-term sustainability at the EU level, will avoid wasteful fragmentation and duplication of time and resources, and facilitate the setting up of more patient registries, especially for the rarest and most fragmented diseases throughout Europe. The first step included an inventory of existing RDPR to identify gaps, the EPIRARE Registry Survey. The survey addressed specific characteristics of existing registries, such as scope and aims, legal basis for collection of data, measures for data protection, organisational and financial support, number of patients registered, unmet needs, data collected, means of

collection, data sources and quality of data, as well as ethical standards. The EPIRARE Registry Survey targeted the largest possible number of research, academic and industry registries to understand the state of the art from the perspective of registry holders.

A parallel EPIRARE Patient Survey was conducted by EURORDIS in order to specifically identify patient registry initiatives and collect the experience and expectations of patient organisations in this field. The analysis that follows in this publication includes the results of the EPIRARE Patient Survey and major trends observed in the experience and expectations of patients and their representatives in RDPR. Some comparisons of these results with those of the EPIRARE Registry Survey were also possible. Finally an investigation into potential differences in opinions between countries, diseases and additional characteristics of the disease (age of onset, prevalence and genetic nature) was also conducted.

As one of the major partners in the EPIRARE project, EURORDIS defined possible policy scenarios on the scope, common data set, governance and sustainability of RD patient registration described in the discussion and conclusions of this text. This essential prerequisite to define national, European and international strategy and concrete actions on patient registries will provide the European Commission with robust elements and consensus amongst stakeholders to define the future policy for the EU registration of rare disease patients.

THE PATIENT'S VOICE

The importance, obstacles and success of RDPR have been reported by professionals.[10, 11] To date the patient's perspective on patient registries has been less documented. To go beyond patients' anecdotes and investigate experience-based opinions in a quantitative way, the results of the EPIRARE Patient Survey will contribute to shaping patient-centred public health policies by describing and comparing patients' experiences and expectations regarding patient registration.

Given the importance of RDPR and within the perspective of creating a European Platform for Rare Disease Registries, EURORDIS has gladly accepted an opportunity to convey a unified patient voice in shaping regional, national and European policy on RDPR. Already, the significance of involving patients and their representatives in providing these recommendations acknowledges the importance of their role for success. Although the EPIRARE Patient Survey is not an exhaustive analysis opinions and expectations on RDPR, it is a valid synthesis of patient opinion, which should be included in the debate. The information provided in this book should be used as an information and advocacy tool in which the collective opinion of over 3,000 rare disease patients is expressed.

1 - Orphanet. Report on Rare Disease Research, Its Determinants in Europe and the Way Forward, May 2011 // 2 - http://www.orpha.net/orphacom/cahiers/docs/GB/Registries.pdf // 3 - Brussels, 25.1.2012. COM (2012) 11 final 2012/0011 (COD) Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the protection of individuals with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation) // 4 - EUCERD RECOMMENDATIONS on RARE DISEASE EUROPEAN REFERENCE NETWORKS, http://www.eucerd.eu/?post_type=document&p=2207 // 5 - to be considered by the PARENT Joint Action, http://www.patientregistries.eu/ // 6 - European Commission. COM (2008) 679 Communication from the Commission to the European Parliament, the Councils the Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europe's challenges. // 7 - Council Recommendation of 8 June 2009 on an action in the field of rare diseases. // 8 - Full declaration in Appendix 2 and http://download.eurordis.org/documents/pdf/EURORDIS_NORD_CORD_JointDec_Registries_FINAL.pdf // 9 - Full Recommendation in Appendix 1 and http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf // 10 - Groft, et al. (2011). The case for a global rare-diseases registry. Lancet, 337(9771): 1057 – 1059. // 11 - Gliklich RE, Dreyer NA, eds. (2010) Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. AHRQ Publication No.10 EHC049. Rockville, MD: Agency for Healthcare Research and Quality.

METHODOLOGY

SCOPE

In order to gather the perspectives and expectations of one of the main stakeholders involved in the discussion of RDPR, EURORDIS designed an online survey, the EPIRARE Patient Survey, specifically targeted towards patients. In parallel, another EPIRARE survey conducted by the ISS targeted registry holders (referred to from here on as the EPIRARE Registry Survey, 64 questions). The EPIRARE Patient Survey was much shorter in length (14 questions and one open-ended comment) and focused on issues closer to patients' interests and expectations. The questionnaire was made available to the rare disease patient community using the online survey tool, Survey Monkey®. Responses to the questionnaire were strictly anonymous and results were treated accordingly. RD National Alliances were instrumental in communicating on the existence of the survey to their constituents and encouraging participation. The survey was conducted from July 1st, 2012 until February 1st, 2013.

QUESTIONNAIRE DESIGN

The EPIRARE Patient Survey was designed to overlapping with some of the issues addressed in the EPIRARE Registry Survey in order to allow a comparison of data from the two different target populations. The topics covered in the EPIRARE Patient Survey were as follows:

- Disease of interest and country of residence
- Aims of a registry
- Type of information collected in a registry
- Registry users
- Access to registry data
- Registry closure
- Information communicated upon enrolment in a registry
- Withdrawal from a registry
- Registry governance
- Initiative for establishing a registry
- Long-term financial sustainability of the registry
- Registry's annual budget
- Rare disease registries at the national and European level

The multiple choice questions were formulated to gather as much information while limiting the length of the survey and avoiding as much technical jargon as much as possible.

The online survey was made available in 10 languages: English (EN), French (FR), Italian (IT), German (DE), Spanish (ES), Portuguese (PT), Greek (EL), Romanian (RO), Czech (CS) and Danish (DA). Translations were performed and validated by respective RD National Alliances and EURORDIS bilingual staff (see Acknowledgements).

DESCRIPTIVE ANALYSIS

Selection of Exploitable Data

The original dataset included 4256 responses. The response distribution was analyzed and upon observing a bimodal distribution of responses all questionnaires with at least one question answered (i.e. at least 6 response units, as some questions are made up of several responses) were included in the analysis in an effort to maximize the total number of exploitable data. Using this threshold, 819 records were eliminated and 3437 questionnaires were included in the analysis. Over 2/3rd of the records eliminated from analysis represented respondents that opened the survey online and disconnected without responding. An inadequate number of responses were recieved regarding a registry's annual budget for analysis.

Languages and Countries

The EN, FR and IT versions were launched first, the DE, ES, PT followed shortly and lastly by the EL, RO, CS and DA versions. Staggered launch dates for translated questionnaires may have influence response rates per country. We do, however, observe high response rates in languages that were launched last, therefore other factors, such as the involvement of RD National Alliances in disseminating the survey may be at play.

Respondents were asked to identify their country of residence. Some respondents did not respond to the survey in their native language, although this did not interrupt the interpretation of results. Response rates per country and per language are described below.
For global responses to a question, responses from all countries both in Europe and beyond were included. Results by country were only analysed for countries in Europe for which more than 80 responses were received. The following country codes were used in the presentation of results by country (Table 1).

Table 1. Country codes used in the presentation of results

BEL	Belgium	**GBR**	United Kingdom
CZR	Czech Republic	**GRC**	Greece
DEU	Germany	**HUN**	Hungary
DNK	Denmark	**ITA**	Italy
ESP	Spain	**PRT**	Portugal
FRA	France	**ROM**	Romania

Diseases

Many diseases were represented by only a few respondents (88 diseases with only two respondents and 233 with only one respondent) making disease-specific analysis for these diseases not possible. As RD National Alliances and organisations played a key role in motivating their constituents in participating in the survey, some groups of respondents by disease were all from the same country. In these cases it was not possible to conclude that opinions were influenced by disease needs rather than geographical context. As such, only diseases with at least 50 respondents and for which not more than 50 % of respondents represented one country were described in the disease-specific results (Table 2).

Williams syndrome	**WS**	117
Behçet syndrome	**BS**	112
Scleroderma	**SCD**	77
Cystic fibrosis	**CF**	65
Duchenne muscular dystrophy	**DMD**	67
Hereditary (familial) spastic paraplegia	**HSP**	54
Neurofibromatosis	**NF**	54
Ehlers-Danlos syndrome	**EDS**	52
Proximal spinal muscular atrophy	**SMA**	51
Tuberous sclerosis	**TS**	50

Table 2. Diseases and disease codes used in the presentation of results

Respondents were asked to identify the disease with which they were affected in an open ended question. Coding of these entries was performed post hoc based on the OrphaCode. Based on Orphanet[1] disease descriptions additional characteristics for each disease were defined including age of onset, prevalence and genetic nature. General results were subsequently analysed according these disease characteristics to investigate their relationship to responses. For diseases with several possibilities of inheritance, the most prevalent genetic nature was selected.

Presentation of Results

Global results are presented using a colour range from red to green where, in general, red represents increased preference and green represents decreased preference amongst respondents. To best illustrate results, an appropriate numerical scale was created to correspond to the colour scale. Despite differences in numerical scales, the same green-to-red colour scale was used for all figures to enable readers to easily see differences across countries, diseases and additional disease characteristics. We use the following example to illustrate the presentation of results throughout this publication (Figure 1).

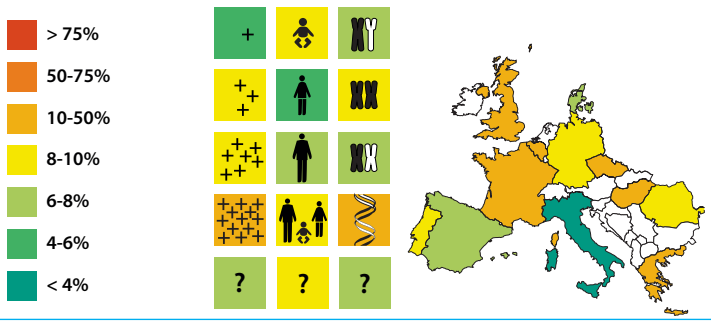


Figure 1. Example of presentation of general results throughout the publication.

To illustrate variation in responses across countries, a map depicts less frequent to more frequent preferences using the colour scale. Genetic nature, prevalence and age of onset are illustrated with the following corresponding definitions:

- **Low prevalence** (<0.5 per 10,000)
- **Medium prevalence** (0.5 per 10,000 – 1 per 10,000)
- **High prevalence** (1 per 10,000 – 5 per 10,000)
- **Over prevalence** (>5 per 10,000)
- **Unknown prevalence**
- **Neonatal/infancy onset**
- **Childhood/adolescence onset**
- **Adulthood onset**
- **Variable age of onset**
- **Unknown age of onset**
- **X-linked**
- **Autosomal recessive**
- **Autosomal dominant**
- **Other genetic** (mitochondrial genetic + sporadic)
- **Non-monogenic/Unknown genetic** (multigenetic +mutifactorial + not genetic + unknown)

Country-specific and disease-specific results are illustrated using bar graphs in which respondents of one country or disease are compared to all other respondents per question (Figure 2).

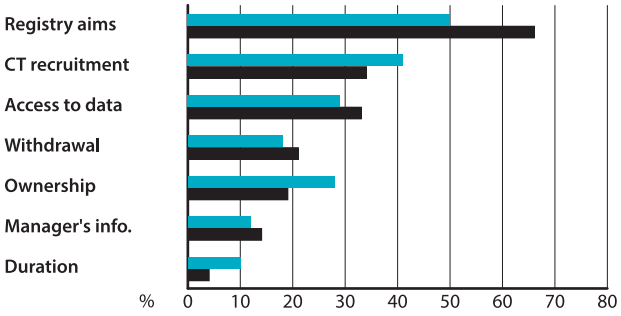


Figure 2.
Example of presentation of disease-specific and country-specific results throughout the publication.

Percentage or score

For several questions participants were asked to select, by decreasing order of preference, three choices. In order to take into account the overall responses and respect the order of preference of respondents, a weighted score was used. For other questions where answers were exclusive (only one choice possible) the results are expressed as a percentage where the total responses add up to 100%. Still other questions provided multiple responses that were non-exclusive for which the results are presented as a percentage and the total may exceed 100%.

Clinical Picture

Sources used in creating clinical descriptions preceding disease-specific results include the, Orphanet[1] and the US National Institutes of Health's Office of Rare Diseases Research (ORDR)[2], as well as validation by patient representatives.

Policy Context

Country-specific results were preceded by a description of RDPR landscape in each country. The Orphanet Report Series, "Disease Registries in Europe"[3] and the 2013 Report on the State of the Art of Rare Disease Activities in Europe were consulted as sources for these summaries. The Orphanet report gathers the most up to date information regarding systematic collections of data for a specific disease or a group of diseases. Cancer registries are only included if they belong to the network RARECARE or focus on a rare form of cancer. The second report has been produced by the Scientific Secretariat of the European Union Committee of Experts on Rare Diseases (EUCERD) through the project EUCERD Joint Action: Working for Rare Diseases[4].

EXPLORATORY ANALYSIS

Selection of Exploitable Data

The original dataset included 4256 responses. As in the descriptive analysis, 819 records were eliminated due to incomplete responses. An additional 115 records were eliminated for which no Orphacode exists and 3322 questionnaires were finally included in the exploratory statistical analysis.

By using the Multiple Correspondence Analysis (MCA) technique, possible associations between characteristics of patients and the disease with which they are concerned and preferences about RDPR expressed in the survey were investigated. Specifically, MCA aims to find out the structure of latent relationships among variables, considering all the variables simultaneously. Variables were thus classified into two groups: 1) active variables which represent characteristics of patients/disease and, 2) supplementary variables which represent the responses to each question of the survey (Table 3). Country classification was based on United Nations Classification of European areas. Countries or subarea with a high number of respondents were separated. Active variables created a factorial plane and supplementary variables were projected on to the factorial plane to investigate possible associations.

Country	Age of Onset	Prevalence	Genetic Nature
Northern Europe	Adulthood	Low (0-0.5 per 10,000)	X-linked dominant + X-linked recessive
Eastern Europe	Childhood/adolescence	Medium (0.5-1 per 10,000)	Autosomal dominant
Western Europe (East)	Neonatal/infancy	High (1-5 per 10,000)	Autosomal recessive
Western Europe (West)	Unknown	Over (> 5 per 10,000)	Mitochondrial inheritance + Multigenic + Mutifactorial
Spain	Variable	Unknown	Not genetic + Unknown genetic
Italy			Sporadic
Other Southern Europe			
Not European Country			

Table 3. Definition of active and supplementary variables in Multiple Correspondence Analysis

RESPONSE DYNAMICS

Response Time

In recognition of all the patients and representatives who volunteered their time to participate in the survey, a rather thorough analysis on response time was performed. Amongst the questionnaires included in the analysis, 50% of the respondents spent between 7 and 16 minutes and 90% spent between 3 and 59 minutes filling out the questionnaire. The median response time was 10 minutes.

Excluding any respondents who took more than three hours to complete the survey (which could be explained, for example, by the need to interrupt the survey, further reflect on the answers or accessing the survey at separate times) the cumulative time spent by volunteers completing the survey was 797 hours, equivalent to more than one month non-stop or almost 5 months of 40-hour work weeks!

Response Rates

Overall, response rates ranged from 99.7% for Question 2 to 74.3% for Question 13. In general, a linear decrease in response rate was observed with each question in the survey (Figure 2). In conclusion, little response fatigue was observed and overall respondents did not exhibit problems answering all questions in the survey.

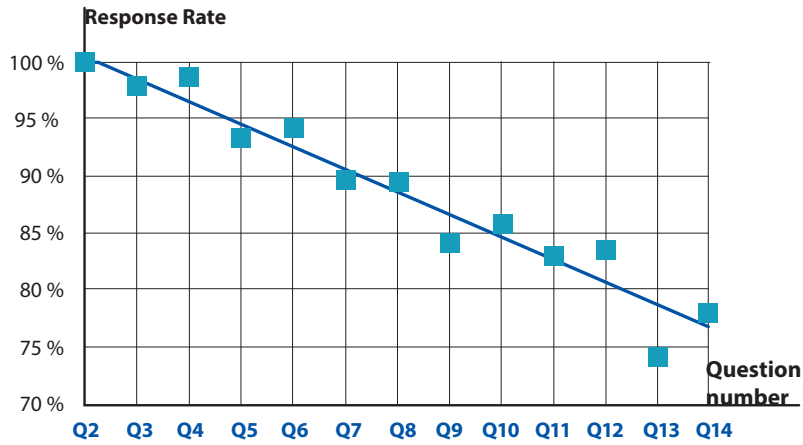


Figure 3.
Response rates per survey question

Responses by Language

The greatest absolute number of respondents filled out the questionnaire in ES, IT, DE, FR and EN (Table 5).

	CS	DE	DA	EL	EN	ES	FR	HU	IT	PT	RO	Total
Total respondents	100	612	185	184	355	1089	492	114	879	207	56	4256

Table 5. Total responses by language

Communication on the availability of the online questionnaire was continuous throughout the survey period and created a very dynamic experience for the patient community that followed its evolution. With each translation of the survey, RD National Alliances were instrumental in encouraging participation. Key communication dates included:

- English, French and Italian **6 June 2012**
- EURORDIS newsletter article inviting participation **01 July 2012**
- Portuguese **19 July 2012**
- Spanish **31 August 2012**
- German **17 September 2012**
- Greek **20 October 2012**
- Romanian **5 November 2012**
- Czech **6 November 2012**
- Danish **15 November 2012**
- Preliminary results published in EURORDIS newsletter and invitation for continued participation **12 December 2012**
- Continued communication via EURORDIS Facebook and Twitter accounts

Increases in survey responses correspond to this communication as illustrated in Figure 4. Survey progress was displayed on the Survey Monkey webpage to encourage continued participation.

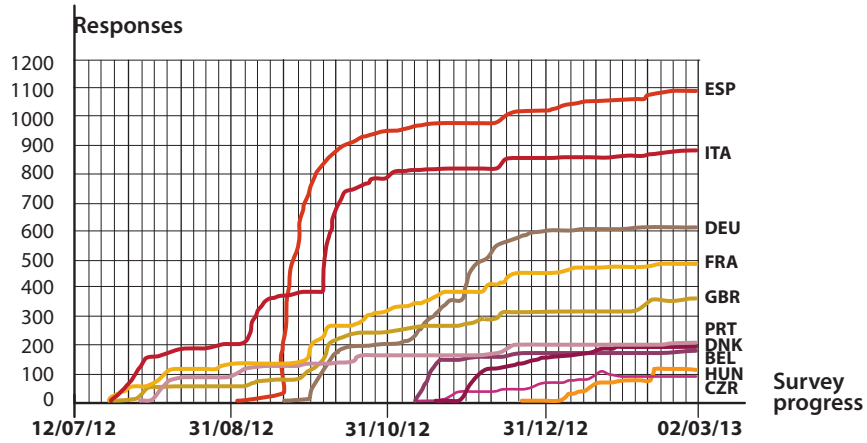


Figure 4.
Access to survey per language

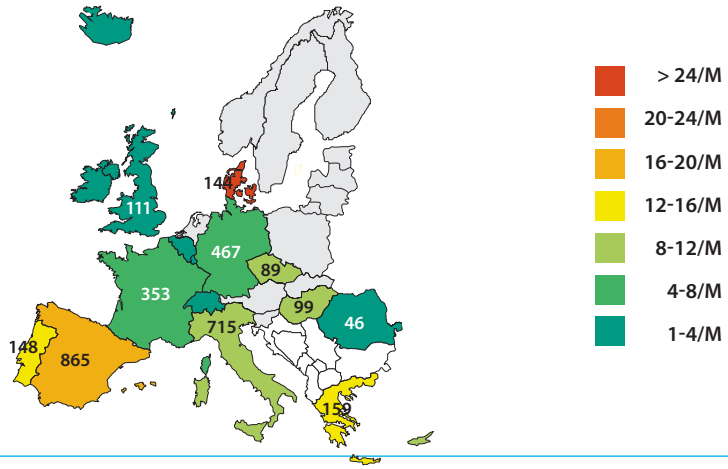
Responses by Country

Of the 3437 responses included in the analysis, 3307 represent respondents from Europe (32 countries) and 130 respondents from countries outside Europe. The highest number of responses came from ESP, ITA, DEU and FRA (Table 6). However, when presented as a ratio of the total number of possible responses (estimated as the country population) we observe how strongly the responses in each language represent the overall opinion of citizens (Figure 5). For example, as compared to FRA (353 total respondents) fewer respondents from HUN (99 respondents) filled out the questionnaire, however the HUN respondents represent a much larger proportion and thus may be more representative of the Hungarian perspective than FRA respondents are of the French perspective. Countries in light blue represent those in which RD National Alliances and organisations were involved in the implementation of the survey (ie. communicating of its availability online to constituents). As a result these countries represent those from which a greater number of responses were gathered.

Table 6.
Total responses per country in Europe

ESP	865	BEL	41	ARM	1	
ITA	715	CHE	15	BGR	1	
DEU	467	NLD	12	BIH	1	
FRA	353	IRL	11	HRV	1	
GRC	159	CYP	5	ISL	1	
PRT	148	AUT	4	LUX	1	
DNK	144	FIN	4	MLT	1	
GBR	111	SWE	4	POL	1	
HUN	99	AND	2	SRB	1	
CZR	89	NOR	2	SVK	1	
ROM	46	RUS	2			

Figure 5.
Ratio of responses per country per million country inhabitants



Responses by Disease

Of the total exploitable responses, 115 disease entries were not able to be coded. Although these entries were included in the global results, they were not included in the analysis of responses by disease.

Overall, 500 diseases were represented in the survey. Several responses represented disease groups, syndrome groups or symptoms (ie. epilepsy, migraine). The number of respondents per disease varied greatly where:

- 13 diseases represented 25% of respondents
- 43 diseases represented 50% of respondents
- 125 diseases represented 75 % of respondents

Many diseases were represented only by a few respondents (88 diseases with only 2 respondents and 233 with only one respondent) making disease-specific analysis for these diseases impossible. The full list of diseases covered by total survey respondents are visually represented on page 8.

1 - www.orpha.net // 2 - www.rarediseases.info.nih.gov // 3 - "Disease Registries in Europe", Orphanet Report Series, Rare Diseases collection, January 2013 // 4 - Aymé S., Rodwell C., eds., "2013 Report on the State of the Art of Rare Disease Activities in Europe", July 2013. Project: EUCERD Joint Action: Working for Rare Diseases N° 2011 22 01, Coordinator: Kate Bushby, University of Newcastle, United Kingdom.

GLOBAL RESULTS

SUMMARY

It is clear from the sample of responses (representing 32 European countries and 543 RD) to this survey treating the very specific topic of "Rare Disease Patient Registries" that European patients living with RD have clear opinions on the subject. Survey participants reported on their opinions about three main characteristics of a RDPR:

1. Structural elements
2. Patient participation
3. Governance and Sustainability

For each characteristic several questions were asked and the responses to individual questions are described below.

Overall, respondents expressed a preference for RDPR that allow the generation of disease knowledge for the development of appropriate care guidelines and policies in addition to treatment evaluation. Respondents reflected a strong preference to make the most of their data, even when a registry closes or when they choose to withdraw. To be best informed about their participation, respondents particularly preferred receiving information about the registry's aims, contact information for the registry manager and procedures for access to data. Similarly, a large majority of respondents underscored the importance of patient representation in the governance of RDPR – particularly to input on elements such as its aims, ethical and legal issues and data access policies. Above all, respondents reported the importance for patient organisations and patients themselves to have access to their own data alongside clinical researchers, healthcare professionals and health authorities.

The participants of this survey also understood and supported the added-value of a comprehensive European approach in the development, maintenance and sustainability of RDPR. Respondents strongly expressed their expectation that legal aspects regarding RDPR development be regulated at the EU level. They equally strongly expressed their expectation for the establishment of a primarily publically-funded common portal for all RDPR supported by the European Commission and Member States.

AIMS OF A REGISTRY

The aims of a registry constitute one of its core characteristics. Patient knowledge and expectations on this aspect are, as such, also fundamental. Overall, survey respondents ranked the importance of registry aims as follows: 1) Healthcare and social services planning for patients (43.2%); 2) Evaluation and monitoring of the efficacy/safety of a treatment (33.8%); 3) Description of the disease (30.4%).

HEALTHCARE AND SOCIAL PLANNING

Healthcare and social planning was reported by 43.2% of respondents as an important aim. German respondents reported this preference less frequently (18.5%) as compared to others.

EVALUATION AND MONITORING OF TREATMENTS

Evaluation and monitoring of treatments was reported by 33.8% of respondents as an important aim. Romanian respondents reported this preference more frequently (60.9%) than others. Danish respondents reported it less frequently as did respondents affected by diseases with unknown prevalence (28.9%) and autosomal dominant (29.7%) inheritance patterns.

DESCRIPTION OF THE DISEASE

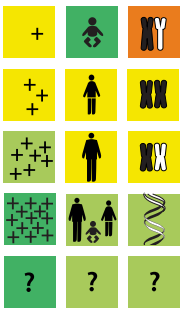
Description of the disease was reported by 30.4% of respondents as an important aim. This was more frequently reported by French (38.5%) and Belgian (37.4%) respondents. Romanian respondents (23.9%) less frequently reported this as did respondents affected with diseases with a childhood/adolescence age of onset (26.4%).

> 40%
35-40%
30-35%
25-30%
20-25%
15-20%
< 15%

EPIDEMIOLOGICAL RESEARCH

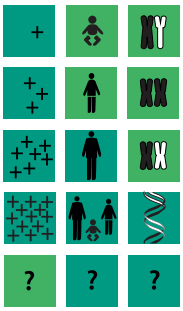
Epidemiological research was reported by 25.8% of respondents as an important aim. This was more frequently reported by Danish (31.0%) and Spanish (30.3%) respondents and less frequently by Hungarian (12.8%) and Czech (13.5%) respondents.

RECRUITMENT FOR CLINICAL TRIALS



Support for clinical trial recruitment was reported by 24.2% of respondents as an important aim. German respondents (32.4%) and respondents affected by diseases with X-linked patterns of inheritance (35.2%) reported this preference more frequently than others.

GENETIC MUTATIONS



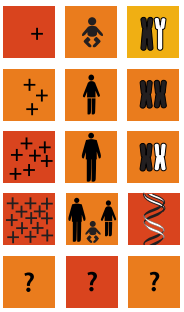
Genetic mutations were reported by 14.5% of respondents as an important aim. This was more frequently reported by Portuguese respondents (17.9%) and respondents affected by diseases with low (17.4%) or unknown (16.7%) prevalence and those with known genetic patterns of inheritance.

TYPES OF INFORMATION COLLECTED IN A REGISTRY

Much like a registry's aims, the type of information collected in a registry has broad implications in terms of its aims and utility, but also influences the governance, sustainability and direct patient experience including the safeguards required. Overall, survey respondents ranked the importance of the types of information as follows:
1) medical information (39.1%);
2) patient-reported outcomes (36.1%); and
3) use of therapeutics (32.2%).

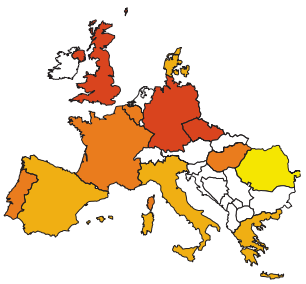
MEDICAL INFORMATION

Medical information was reported as important to collect by 39.1% of respondents. This was less frequently reported by Portuguese (29.5%) respondents. Little variability was observed across disease characteristics.



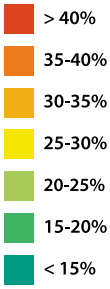
PATIENT-REPORTED OUTCOMES

Patient reported outcomes were reported as important to collect by 36.1% of respondents. This was more frequently reported by respondents affected by diseases with unknown prevalence (41.2%) and unknown age of onset (40.3%) and less frequently by Romanian respondents (25.2%).



THERAPEUTIC USE

Information on therapeutic use was reported as important to collect by 32.2% of respondents. This was most frequently reported by Romanian respondents (54.1%).



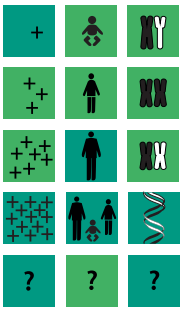
GENETIC INFORMATION

Genetic information was reported as important to collect by 31.0% of respondents. Responses varied considerably across countries and disease characteristics.

PARTICIPATION IN CLINICAL RESEARCH AND BIOBANKS

Information on participation in clinical research and biobanks was reported as important to collect by 27.3% of respondents. This was more frequently reported by respondents affected by X-linked diseases (33.0%) and those with adult age of onset. Romanian (30.3%)respondents less frequently reported this as important information to collect.

PERSONAL INFORMATION



Personal information was reported as important to collect by 15.4% of respondents. Little variability was observed across countries or disease characteristics.

INFORMATION COMMUNICATED UPON ENROLMENT IN A REGISTRY

The information provided to a patient in order to make an informed decision about participating in a registry has great ethical and legal implications. Overall, survey participants ranked the following types of information in order o f importance for true informed consent:
1) registry aims (66.0%);
2) possibility of being contacted for participation in clinical trials (34.2%); and
3) information on access to data (32.9%).

REGISTRY AIMS

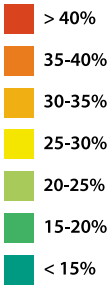
Upon enrolling in a registry, 66.0% of respondents reported a preference for being informed about the registry's aims. This was less frequently reported by respondents affected by diseases with a higher prevalence (57.9%).

RECRUITMENT FOR CLINICAL TRIALS

Upon enrolling in a registry, 34.2% of respondents reported a preference for being informed about the possibility of being contacted for participation in clinical trials. German respondents (46.9%) and respondents affected by X-linked diseases (40.7%) reported this preference more frequently.

ACCESS TO DATA

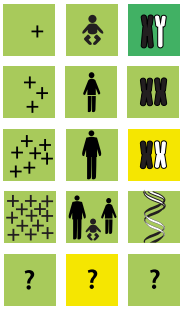
Upon enrolling in a registry, 32.9% of respondents reported a preference for being informed about the access to data. Respondents from the United Kingdom (50.4%) reported this preference more frequently, whereas respondents affected by X-linked diseases (29.5%) responded less frequently.



RIGHT TO WITHDRAW

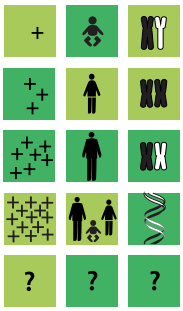
Upon enrolling in a registry, 21.1% of respondents reported a preference for being informed about the right to withdraw. Belgian respondents (34.3%) reported a higher preference for this information as compared to others.

DATA OWNERSHIP



Upon enrolling in a registry, 18.8% of respondents reported a preference for being informed about data ownership. Belgian respondents (30.5%) reported a particularly high preference for this information.

REGISTRY MANAGER'S CONTACT INFORMATION



Upon enrolling in a registry, 14.5% of respondents reported a preference for being informed about a way to contact the registry manager.
Little variability was observed for this preference.

WITHDRAWAL FROM A REGISTRY

The possibility to withdraw from the registry is a given. However, solutions for treating data collected prior to a patient's withdrawal from a registry can present a dilemma.
Survey respondents reported their preferences for handling of data under such circumstances as follows:
1) data anonymised for future research (68.1%);
2) data destroyed (23.3%); and
3) authorisation withdrawn for future use of data (16.6%).

DATA ANONYMISED FOR FUTURE RESEARCH

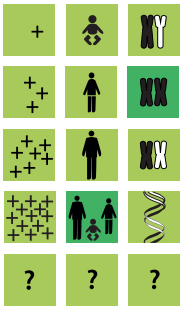
Upon withdrawing from a registry, 68.1% respondents reported their preference for having data anonymised for future research. This was more frequently observed amongst Danish (85.3%) and Hungarian (85.1%) respondents. Little variability was observed across disease characteristics.

> 75%
60-75%
25-60%
20-25%
15-20%
10-15%
< 10%

DATA DESTROYED

Upon withdrawing from a registry, 23.3% respondents reported their preference for having data destroyed. This was less frequently observed amongst Romanian (8.9%) respondents

AUTHORISATION WITHDRAWN FOR FUTURE USE OF DATA



Upon withdrawing from a registry, 16.6% respondents reported their preference for having authorisation withdrawn for future use. This was more frequently observed amongst Italian (32.2%) and Portuguese (26.7%) respondents. Little variability was observed across disease characteristics.

REGISTRY CLOSURE

The premature termination of a register's activities is sometimes an unfortunate event that presents ethical and procedural difficulties in handling data. Respondents reflected a strong preference to make the most of their data, even when a registry closes. Very few respondents reported the choice to store their data indefinitely (8.5%), store it for a limited time (8.1%) or destroy their data (6.5%). Rather, the majority of respondents (76.9%) preferred to make their data available to other registries or to the research community.

DATA MADE AVAILABLE TO OTHER REGISTRIES OR THE RESEARCH COMMUNITY

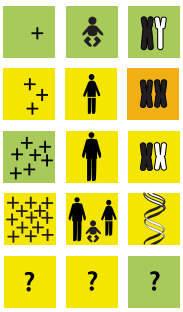
Upon a registry's closure, 76.9% of respondents reported a preference for making data available to other registries or the research community. Czech respondents (53.3%) reported this preference much less frequently than others. Little variability was observed across disease characteristics.

DATA STORED FOR A LIMITED TIME

Upon a registry's closure, 8.5% of respondents reported a preference for storing data for a limited time. Variability was observed across countries and disease characteristics.

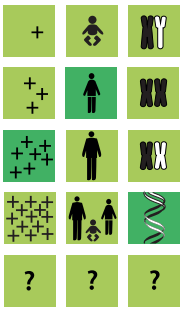
> 75%
50-75%
10-50%
8-10%
6-8%
4-6%
< 4%

DATA STORED INDEFINITELY



Upon a registry's closure, 8.1% of respondents reported a preference for storing data indefinitely. Variability was observed across countries and disease characteristics.

DATA DESTROYED



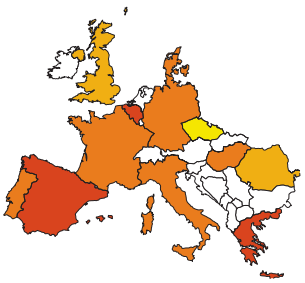
Upon a registry's closure, 6.5% of respondents reported a preference for having data destroyed. Czech (16.9%), United Kingdom (15.2%), and German (10.9%) respondents reported this preference more frequently than others. Little variability was observed across disease characteristics.

INITIATIVE FOR ESTABLISHING A REGISTRY

Patients are becoming increasingly aware of the importance and existence of registries for their disease. In fact, patient associations are more and more often the initiators of the establishment of registries themselves. This was reflected in survey respondents knowledge about the initiators of registries where most frequently (27.8%) respondents who were aware of a registry for their disease knew of one initiated by a patient organisation.

PATIENT ORGANISATION

27.8% of respondents knew of a registry for their disease initiated by a patient organisation. Respondents from the Czech Republic (9.6%) less frequently gave this response.



HOSPITAL

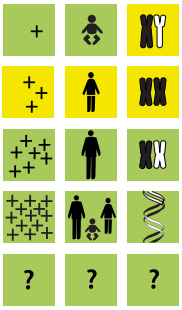
13.3% of respondents knew of a registry for their disease initiated by a hospital. Respondents affected by a disease with unknown prevalence less frequently gave this response, as did German (5.8%) and Italian (9.2%) respondents.

UNIVERSITY/RESEARCH INSTITUTE

13.1% of respondents knew of a registry for their disease initiated by a university or research institute. Belgian respondents (25.0%) more frequently gave this response as compared to other respondents. Little variability was observed across disease characteristics.

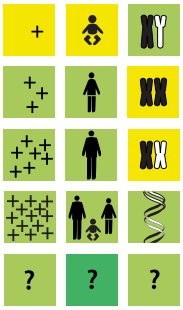
FOUNDATION

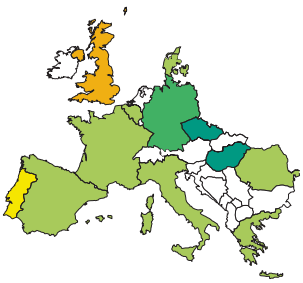
4.6% of respondents knew of a registry for their disease initiated by a foundation. Hungarian respondents (6.6%) most frequently gave this response where as no Belgian or Danish respondents were aware of such a registry.



> 30%
20-30%
10-20%
5-10%
2.5-5%
1-2.5%
< 1%

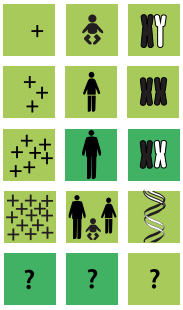
NATIONAL AUTHORITY

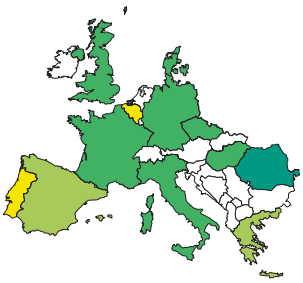




4.3% of respondents knew of a registry for their disease initiated by national authorities. Responses were quite variable across countries and disease characteristics.

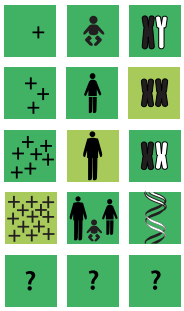
EU COMMISSION/EU AGENCY





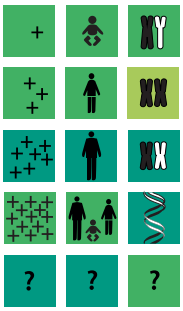
2.8% of respondents knew of a registry for their disease initiated by the EU Commission or Agency.

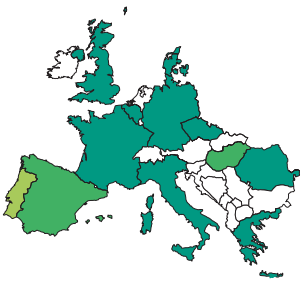
REGIONAL AUTHORITY



2.0% of respondents knew of a registry for their disease initiated by regional authorities. Italian respondents (3.1%) were most often aware of such a registry.

INDUSTRY





1.4% of respondents knew of a registry for their disease initiated by industry. Little variability was observed across countries or disease characteristics.

REGISTRY USERS/ ACCESS

The transparency of potential users of registry data is of paramount importance both for defining its governance mechanisms and the informed consent of participants.
On this issue survey respondents were ranked their preference for access to data by the following users:
1) patient organisations (88.8%);
2) public institutions (64.1%); and
3) public health authorities (44.2%).

PATIENT ORGANISATIONS

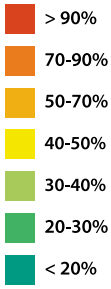
88.8% of respondents answered that patient organisations should have access to registry data. Little variability was observed across countries or disease characteristics.

PUBLIC INSTITUTIONS

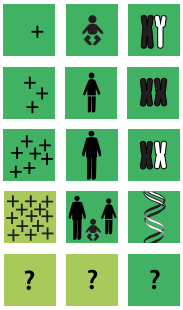
64.1% of respondents answered that public institutions should have access to registry data. French (90.8%) and Belgian (85.4%) respondents more frequently favoured access to data for public institutions whereas Czech respondents (30.2%) less frequently did so.

PUBLIC HEALTH AUTHORITIES

44.2% of respondents answered that public health authorities should have access to registry data. Some variability was observed across countries and little variability across disease characteristics.



PRIVATE INSTITUTIONS/CITIZENS



27.4% of respondents answered that private citizens or institutions should have access to registry data. German respondents (45.5%) particularly favoured access to registry data for private citizens or institutions where as Romanian respondents (6.7%) did not.

INDUSTRY

24.8% of respondents answered that industry should have access to registry data. Spanish respondents (48.1%) were particularly in favour of access to data for industry. Little variability was observed across disease characteristics.

REGISTRY GOVERNANCE

The governance structure of a register reflects the roles and extent of involvement of the different stakeholders. Survey respondents reported a great interest for involvement in registry governance, particularly regarding:
1) registry aims (76.3%);
2) ethical and legal issues (74.0%); and
3) data access (66.9%).

REGISTRY AIMS

For patient representatives on a governance board, 76.3% of respondents indicated the importance of their opinion on a registry's aims. Responses were quite variable across countries and less variable across disease characteristics.

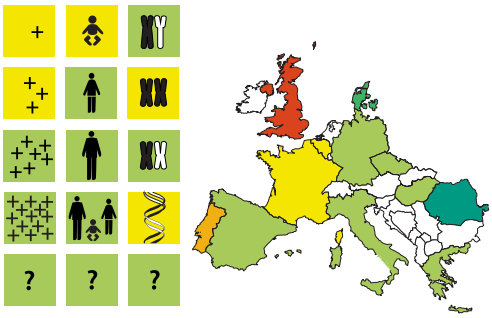
ETHICAL AND LEGAL ISSUES

For patient representatives on a governance board, 74.0% of respondents indicated the importance of their opinion on ethical and legal issues. Responses were quite variable across countries and less variable across disease characteristics.

ACCESS TO DATA

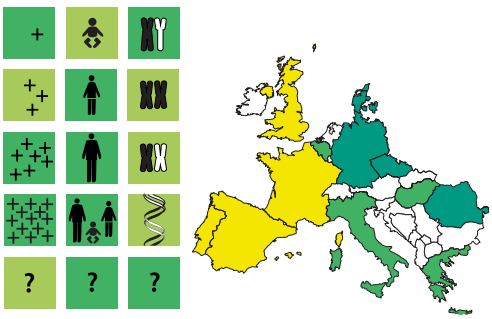
For patient representatives on a governance board, 66.9% of respondents indicated the importance of their opinion on access to data. Respondents from the United Kingdom (79.1%) particularly favoured this response. Little variability was observed across disease characteristics.

COMMUNICATION WITH USERS



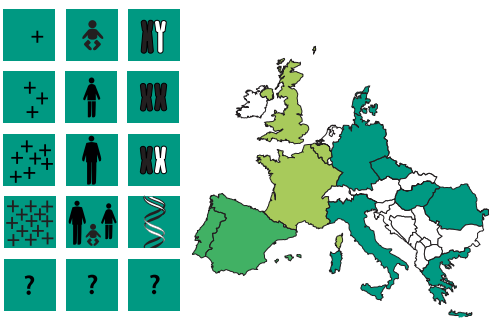
For patient representatives on a governance board, 64.2% of respondents indicated the importance of their opinion on communication with registry users. Respondents from the United Kingdom (80.7%) particularly favoured this response. Little variability was observed across disease characteristics.

STAKEHOLDER ALIGNMENT



For patient representatives on a governance board, 59.9% of respondents indicated the importance of their opinion on coordination with stakeholders. German respondents (45.2%) less frequently favoured this response. Less variability was observed across disease characteristics.

FINANCIAL AND ADMINISTRATIVE ISSUES



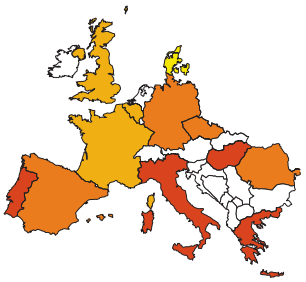
For patient representatives on a governance board, 51.2% of respondents indicated the importance of their opinion on financial and administrative issues. German respondents (37.6%) less frequently favoured this response. Little variability was observed across countries and disease characteristics.

LONG-TERM FINANCIAL SUSTAINA-BILITY OF A REGISTRY

The long-term financial sustainability of a register is a fundamental aspect for ensuring the appropriate achievement of the registry's aims. Patients and their representatives are particularly eager to see that the responsibility to ensure the long-term activity of a registry is delegated to the most appropriate stakeholder(s). Respondents of the survey reported their opinion that the EU Commission/ EU Agency (42.0%), universities or research institutes (40.2%) and patient organisations (39.0%) are best suited in this role.

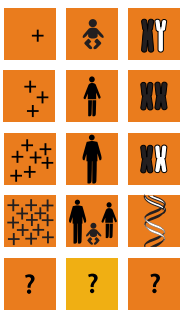
EU COMMISSION/EU AGENCY

42.0% of respondents indicated that in their opinion the EU Commission or an EU agency could best ensure the sustainability of a registry. Respondents from Denmark (23.5%) less frequently reported this opinion.



NATIONAL AUTHORITY

40.2% of respondents indicated that national authorities could best ensure the sustainability of a registry. German respondents (18.5%) less frequently reported this opinion.

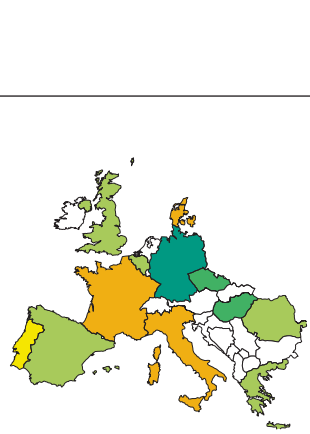


UNIVERSITY/RESEARCH INSTITUTE

39.0% of respondents indicated that universities or research institutes could best ensure the sustainability of a registry. Romanian respondents (12.4%) less frequently reported this opinion while German respondents (51.1%) reported it more frequently.

PATIENT ORGANISATION

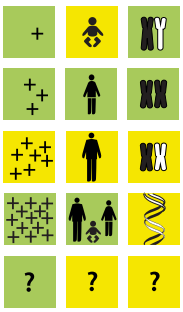
27.5% of respondents indicated their opinion that patient organisations could best ensure the sustainability of a registry. Variability was observed across countries but not across disease characteristics.



HOSPITAL

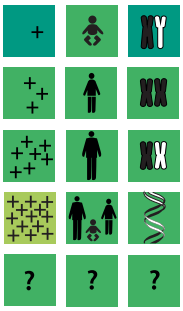
20.1% of respondents indicated their opinion that hospitals could best ensure the sustainability of a registry. Respondents affected by disease with a higher prevalence (30.6%) more frequently reported this opinion. Variable opinions were reported across countries.

FOUNDATION



19.3% of respondents indicated their opinion that foundations could best ensure the sustainability of a registry. Variable opinions were observed across countries and disease characteristics.

REGIONAL AUTHORITY



11.8% of respondents indicated their opinion that regional authorities could best ensure the sustainability of a registry. Italian respondents (24.0%) more frequently reported this opinion.

INDUSTRY/INDUSTRY ASSOCIATION

11.4% of respondents indicated their opinion that industry could best ensure the sustainability of a registry. Little variability was observed across countries or disease characteristics.

RARE DISEASE PATIENT REGISTRIES AT THE EUROPEAN LEVEL

To explore the feasibility of the creation of a European reference platform from the patient's perspective, survey respondents were asked about their expectations for a European approach in the development, management and sustainability of RDPR.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

Overall, the overwhelming majority of respondents (84.8%) reported being in favour of a uniform legislative framework for RDPR across Europe, where only 4.3% did not agree and only 10.9% had no opinion. Variability was observed across countries where Romanian (95.3%), Portuguese (92.9%), Italian (92.4%) and Spanish (91.8%) respondents were particularly in favour of this proposal and United Kingdom (73.1%), Danish (67.2%), and Czech (60.0%) respondents were less so. Less variability was observed across disease characteristics, although respondents affected by diseases with low prevalence (86.3%) and a genetic basis more frequently reported agreement with this proposal.

«I have experienced the difficulties of creating a register for the less prevalent diseases. The lack of coordination at the local, national and European levels makes many projects non-viable. A strong European authority will be really beneficial by forcing local institutions to adapt the registers to a platform that makes effective communication possible, which is not the case today with programs running under FP7, where the obligation to share data, develop open protocols, communicate with other stakeholders, etc. is totally absent.»

«It is not only important to learn about a single rare disease, but the aggregate information about all rare diseases would give us a broader perspective on groups of related diseases that might provide the clues needed to fix them.»

COMMON EUROPEAN REGISTRY INFRASTRUCTURE

An overwhelming majority of respondents (90.7%) agreed with a common European registry infrastructure. Only 2.8% disagreed and 6.5% had no opinion regarding this proposal. Variability was observed across countries where Hungarian (94.4%), Spanish (94.2%), Greek (93.2%), Italian (92.1%) and Portuguese (92.1%) respondents were particularly in favour of this proposal and United Kingdom (78.6%) respondents were less so. Almost no variability was observed across disease characteristics although respondents affected by diseases with low prevalence (93.6%) and unknown prevalence (93.0%) were slightly more in favour.

«A register would be really helpful for everyone: patients, hospitals, research institutes etc. In addition to the financial level, one should encourage everyone to cooperate to make sure to keep the registers updated on diseases, treatments and possible research and trials, so as to give a clear, global vision to those who need it most.»

«Europe being united, we should work together and collaborate on possible studies at European level, and on both scientific and social issues, as well as provision of information to citizens.»

«It is crucial for rare disorders/diseases to have a platform through which they become better known and to enable the transfer of information between different countries. There is no point reinventing the wheel - if someone has information useful to others, it makes sense to share it.»

RESULTS BY COUNTRY

BELGIUM

Regional registries	2
National registries	16
European registries	2
Global registries	1
Total number of registries	21

BELGIAN REGISTRIES LANDSCAPE

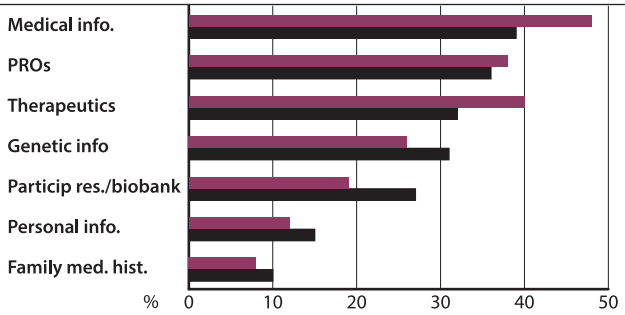
In December 2011 the Scientific Institute of Public Health was awarded the 2012-2013 budget for a Central Registry for Rare Diseases. First steps included the mapping of expertise in RD in Belgian hospitals including further mapping and characterisation of RD patient databases, defining criteria for prioritisation in elaborating new disease-specific registries, participation in EPIRARE, defining the common data set and developing a business plan and privacy plan for a central registry. Until these advances, nationally-funded patient registries only existed for Cystic fibrosis and some neuromuscular diseases. Belgian registries currently contribute to the following European registries: EUROCAT, AIR, ECFS, RBDD, ESID, EIMD, ENRAH, EUROGLYCANET, EUNEFRON and EURECHINOREG.

PARTICIPANTS IN THE SURVEY

A total of 41 survey respondents answered from Belgium representing 1.2% of total survey responses. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Belgium are presented. For the remainder of survey questions, Belgian respondents did not differ significantly in their responses as compared to the general results.

Amongst the 22 diseases represented by responses from Belgium, the most represented were Scleroderma (15), Angelman syndrome (2), Behçet syndrome (2), Hereditary angioedema (2), Wegener granulomatosis (2).

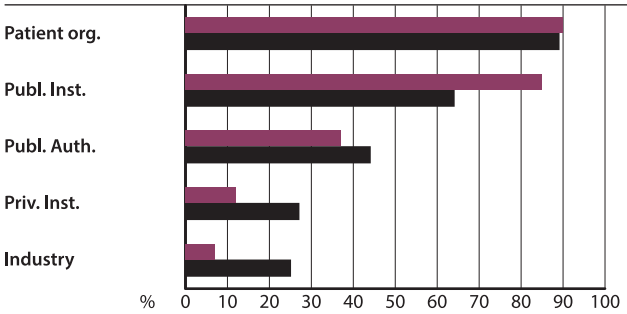
«I welcome anything that will help advance our knowledge on «rare» diseases, which when they affect you personally are no longer rare...»



TYPES OF INFORMATION COLLECTED IN A REGISTRY

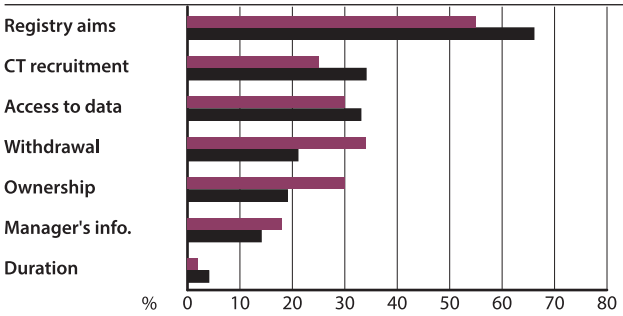
Belgian respondents more frequently communicated the importance of collecting medical information (48.3%) and information on therapeutic use (40.0%) than other respondents. They less frequently communicated the importance of collecting genetic information (25.8%) and patient participation in clinical research or a biobank (19.2%).

REGISTRY USERS/ACCESS



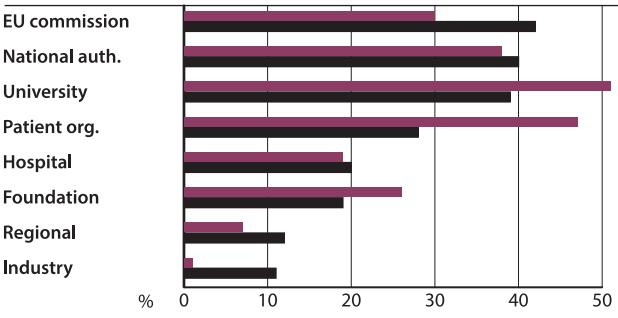
Belgian respondents very frequently expressed a preference for patient organisations (90.2%) and public institutions (85.4%) to have access to registry data. As compared to other European respondents, even less Belgian (7.3%) respondents favoured the access to data for industry.

INFORMATION COMMUNICATED UPON ENROLMENT IN A REGISTRY



Belgian respondents differed in the overall ranking of the types of information communicated to patients participating in registries. The preference for information about withdrawal from the registry (34.3%) and custodianship of the registry (30.5%) was more significantly observed amongst Belgian respondents as compared to respondents from any other country.

LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY



Belgian respondents most frequently favoured universities and research institutes (51.0%) and patient organisations (47.1%) in assuring the long-term financial sustainability of a registry. Only 30.4% favoured the European Commission/EU Agency in assuring this sustainability. Almost no Belgian respondents (1.0%) indicated their preference for industry as a source of long-term sustainability.

COMMON EUROPEAN REGISTRY INFRASTRUCTURE

Belgian respondents agreed less frequently than overall respondents (85.7%) with the establishment of a common portal European Commission and Member States for all RDPR in Europe. A significant number had no opinion (11.4%) and a few (2.9%) disagreed.

CZECH REPUBLIC

Regional registries	0
National registries	4
European registries	0
Global registries	0
Total number of registries	4

CZECH REGISTRIES LANDSCAPE

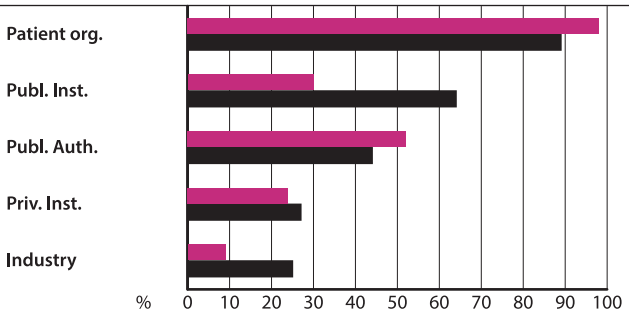
Current shortcomings in RDPR in the Czech Republic exist and as a result no comprehensive information on the prevalence of RD is available. An interministerial and interdisciplinary commission for RD is in the process of establishing a national registry federating RD patient data from the Institute of Health Information and Statistics, the National Register of Reproductive Health. The first steps include a feasibility study in collaboration with the Czech Data Protection Authority. Registries in the Czech Republic currently contribute to EUROCARE CF, EUROCAT, SCNIR registry, EPNET, TREAT-NMD and RD Connect.

PARTICIPANTS IN THE SURVEY

A total of 89 survey respondents from the Czech Republic represented 2.6% of total survey responses. The ratio of responses per million Czech inhabitants was not as low as many other country groups (8.6). As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to the Czech Republic are presented. For the remainder of survey questions, Czech respondents did not differ significantly in their response as compared to respondents from other countries.

Amongst the 34 diseases represented by responses from the Czech Republic, the most represented were Proximal spinal muscular atrophy (13), Prader-Willi syndrome (8), Marfan syndrome (6), X-linked Charcot-Marie-Tooth disease (6), Cystic fibrosis (5), Perineural cyst (5), Hereditary angioedema (4) and Rett syndrome (4).

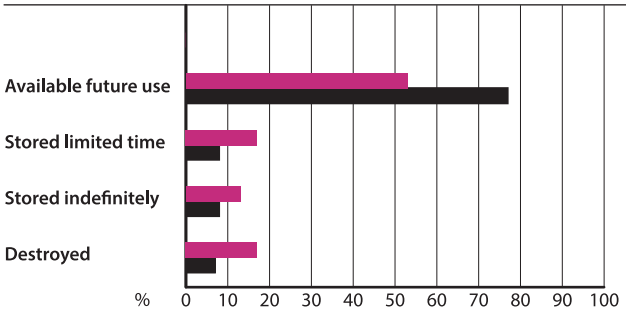
«I think patients and representatives should be involved in drafting legislation about anything that relates to their illness. Patients are the greatest experts on their disease…Even an expert does not perfectly understand all rare diseases.»



REGISTRY USERS/ACCESS

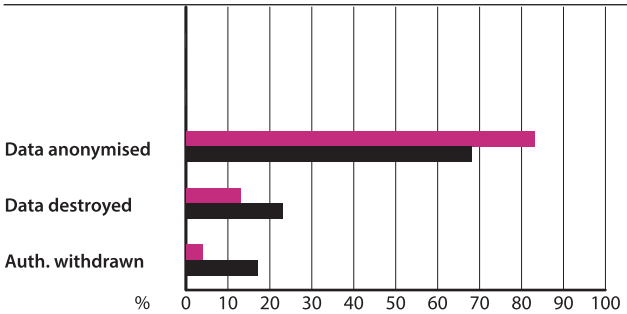
Czech respondents, even more than any other country group, most frequently expressed a preference for patient organisations (97.7%) to have access to registry data.

REGISTRY CLOSURE



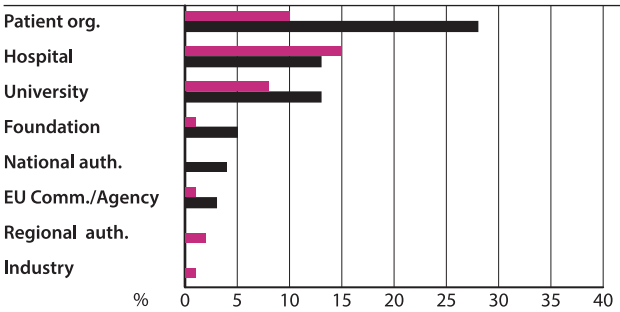
Czech responses reflected a less frequent preference (53.3%) to make data available to other registries or the research community and more frequently preferred data to be stored for a limited time (16.9%) or destroyed (16.9%) upon a registry's closure as compared to most other countries.

WITHDRAWAL FROM A REGISTRY



Czech respondents reported a preference for anonymising their data for future research following the withdrawal from a registry more frequently (83.3%) than respondents from other countries.

INITIATIVE FOR ESTABLISHING A REGISTRY



Czech respondents that knew of the existence of a register for their disease much less frequently reported patient organisations (9.6%) as the initiator of a registry as compared to other countries. Overall, fewer respondents were aware of a registry for their disease.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

Czech respondents agreed less frequently than overall respondents (60.0%) with the proposal of a European legislation to uniformly regulate RDPR across Europe. A significant number had no opinion (22.8%) or disagreed (17.1%).

DENMARK

Regional registries	0
National registries	1
European registries	3
Global registries	0
Total number of registries	4

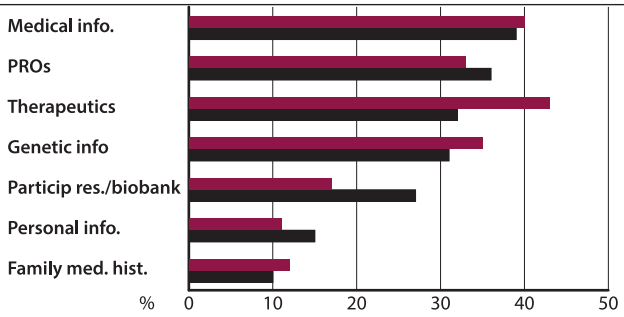
DANISH REGISTRIES LANDSCAPE

The Nordic Council of Ministers has supported the Raredis database, developed in Denmark, since 2007. This database collects clinical data on nearly 1500 RD patients treated for almost 600 RD at the two centres of RD in Denmark. Centres of RD in other Nordic countries use their local version of Raredis for collecting clinical data to contribute. Data can be used for research projects and benchmarking at a Nordic level for different rare diseases. Danish registries contribute to European registries such as EUROCARE CF, EIMD, EMHG and EUROCAT.

PARTICIPANTS IN THE SURVEY

A total of 144 survey respondents from Denmark represented 4.1% of total survey responses.
As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Denmark are presented. For the remainder of survey questions, Danish respondents did not differ significantly in their response as compared to respondents from other countries.
Amongst the 47 diseases represented by responses from Denmark, the most represented were Neurofibromatosis (19), Hereditary spastic paraplegia (16), Rendu-Osler-Weber disease (12), Common variable immunodeficiency (9), Chronic fatigue (8), Friedreich ataxia (8), Prader-Willi syndrome (8) and Hemophilia (5).

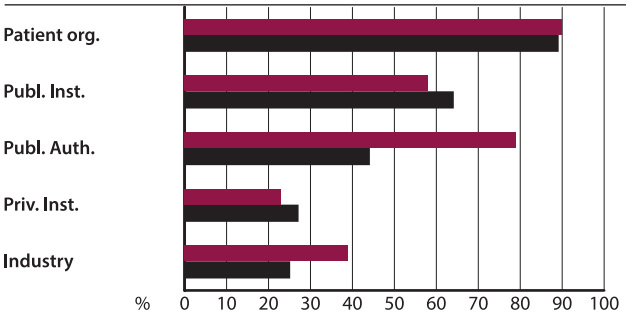
« With a rare disease diagnosis, it is important to have a large dataset that spans multiple countries - these diseases can not be investigated in 10-12 patients in Denmark ... It requires a concerted effort so that all patient data is together and we can observe all their experiences. »



TYPES OF INFORMATION COLLECTED IN A REGISTRY

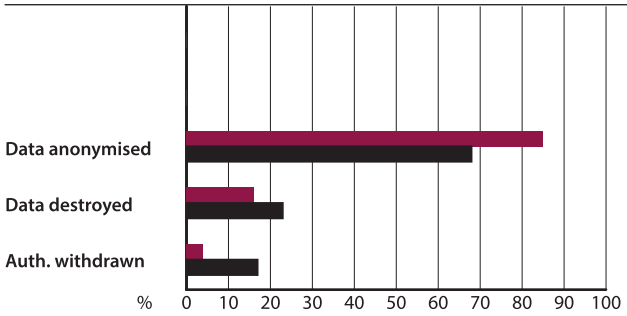
Danish respondents more frequently communicated the importance of collecting genetic information (34.5%) and information on therapeutic use (42.6%) and less frequently communicated the importance of collecting information on patient participation in clinical research or a biobank (17.4%) than most other respondents.

REGISTRY USERS/ACCESS



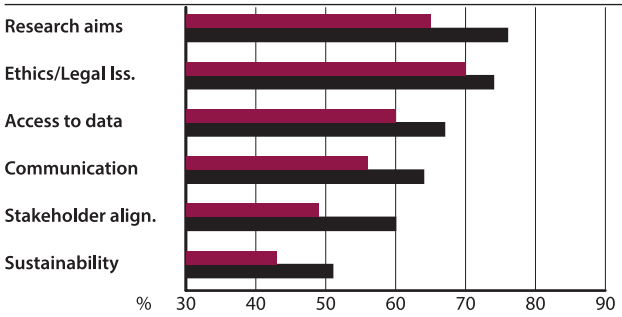
Danish respondents very frequently expressed a preference for patient organisations (90.1%) and public authorities (78.9%) to have access to registry data. As compared to other countries, Danish respondents more frequently favoured the access to data for industry (38.7%) as compared to most other country respondents.

WITHDRAWAL FROM A REGISTRY



Danish respondents reported a preference for anonymising their data for future research following the withdrawal from a registry even more frequently (85.3%) than respondents from other countries.

REGISTRY GOVERNANCE



Overall, Danish respondents less frequently reported the importance of a patient perspective in the governance of a registry as compared to other respondents – even for aspects such as research aims (65.0%), ethical and legal issues (69.8%) and access to data (59.7%).

UNIFORM EUROPEAN REGULATORY FRAMEWORK

Danish respondents agreed less frequently than overall respondents (67.2%) with the proposal of a European legislation to uniformly regulate RDPR across Europe. A significant number had no opinion (22.1%) and a few (10.6%) disagreed.

FRANCE

Regional registries	18
National registries	93
European registries	12
Global registries	5
Total number of registries	128

FRENCH REGISTRIES LANDSCAPE

Many regional, national and international RDPR exist in France. The Second National Plan for Rare Diseases includes the creation of a National Rare Disease Database (BNDMR) whose primary objective is healthcare planning and secondary objective is the recruitment of patients for CT or research cohorts (RaDiCo project). Local and regional centers for RD are the primary sources of data as well as diagnostic laboratories (genetic, cytogenetic, etc.) or existing RDPR where appropriate. France contributes to several European rare disease registries including EUROCAT, EUROHISTIONET, EPI-EPNET, EURECHINOREG, European central hypoventilation syndrome registry, EIMD, EUROWABB, EUROTRAPS, CHS, EUROCARE CF, ECFS, INFEVERS, EDMUS, EHN-EUROHISTIONET, ESCROT-HU, SCLS registry, VALID, TREAT-NMD and RD Connect.

PARTICIPANTS IN THE SURVEY

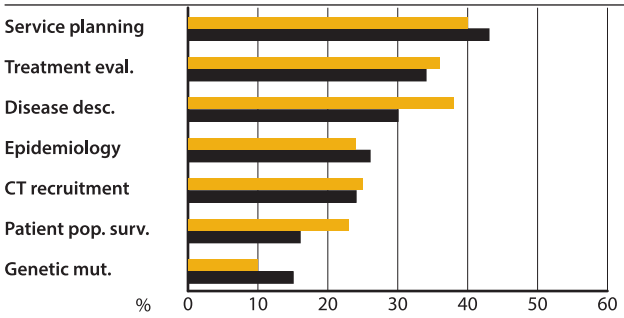
A total of 353 survey respondents were from France representing 10.2% of total survey responses.
This represents one of largest groups of respondents per country. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to France are presented. For the remainder of survey questions, French respondents did not differ significantly in their responses as compared to the general survey results.
The ratio of responses per million French inhabitants was not very high (5.6) suggesting that responses from France less strongly represent the overall opinion of French citizens living with RD as compared to other country groups.
Amongst the 125 diseases represented by responses from France, the most represented include Williams syndrome (32), Proximal spinal muscular atrophy (21), Angelman syndrome (19), Behçet disease (17), Systemic lupus erythematosus (15), Hidradenitis suppurativa (13), Wegener granulomatosis (13) and Autosomal dominant polycystic kidney disease (12).

«It seems to me that doctors in hospitals often tend not to share patient data because they plan to publish articles about them… Doesn't this complicate data sharing in a registry?»

«DNA sequencing opens the door to potential abuses with serious consequences. I am concerned about the use of these data by public authorities or private companies (health insurance companies).

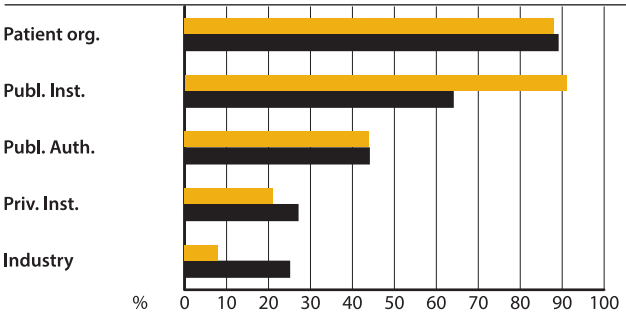
I am convinced of the value of such registries for research and the benefit of patients but want to be sure the data is secured so as not to bring any harm to patients and their families.»

AIMS OF A REGISTRY



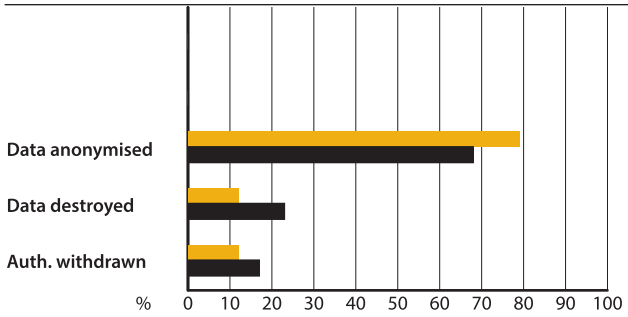
French respondents less frequently reported a preference for healthcare and social services planning (39.6%) as an important registry aim. More frequently than other respondents, French survey participants reported the description of the disease (38.5%) as an almost equally important aim.

REGISTRY USERS/ACCESS



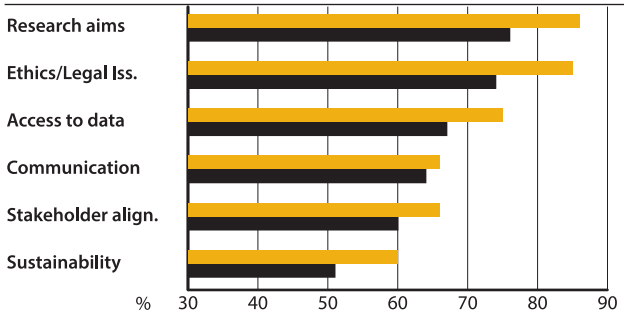
French respondents very frequently expressed a preference for patient organisations (87.7%) and public institutions (90.8%) to have access to registry data. As compared to other European respondents, even less French respondents favoured the access to data for industry (7.7%).

WITHDRAWAL FROM A REGISTRY



French respondents reported a preference for anonymising their data for future research following withdrawal from a registry even more frequently (79.3%) than respondents from other countries.

REGISTRY GOVERNANCE



Overall, French respondents more frequently reported the importance of a patient perspective in the governance of a registry as compared to other respondents – especially for aspects such as research aims (85.7%), ethical and legal issues (85.3%), access to data (74.8%) and information about the registry's sustainability/closure (60.2%).

GERMANY

Regional registries	9
National registries	64
European registries	25
Global registries	7
Total number of registries	105

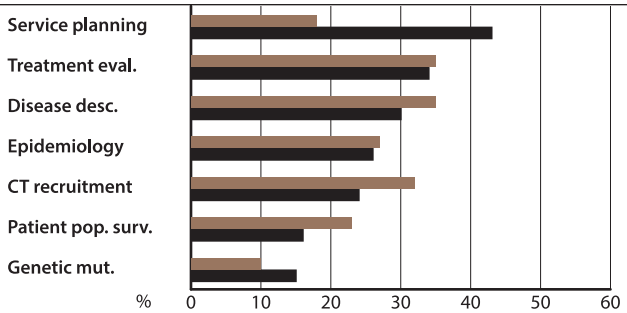
GERMAN REGISTRIES LANDSCAPE

Despite the quite large number of registries in Germany, there is currently no centralised framework to designate or accredit them. All federal states are required to register cancers, (including rare cancers) in existing population based cancer registries, but not other RD. The future national RD action plan will consider the area of registries and a possible minimal data set to be applied. Several German RDPR are implicated in European or international networks including CompERA-XL, CWS-SoTiSaR, DOSAK, CEDATA-GPGE, EUROCAT, TREAT-NMD, EBAR, ENETS, EPICURE, EU-RHAB, EurIPFreg, EHDN, EIMD, EurIPFnet, E-IMD, EURIPEDES, European Alport registry, EuroDSD, EUROSCA-R, EUTOS, Kids Lung Register, KINDLERNET, NCL-Registry, PODONET, Register for rare myeloproliferative neoplasms, RetDis Database, RegiSCAR and RD-Connect.

PARTICIPANTS IN THE SURVEY

A total of 467 survey respondents were from Germany representing 13.4% of total survey responses. This represents one of the largest groups of respondents per country. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Germany are presented. For the remainder of survey questions, German respondents did not differ significantly in their response as compared to respondents from other countries.

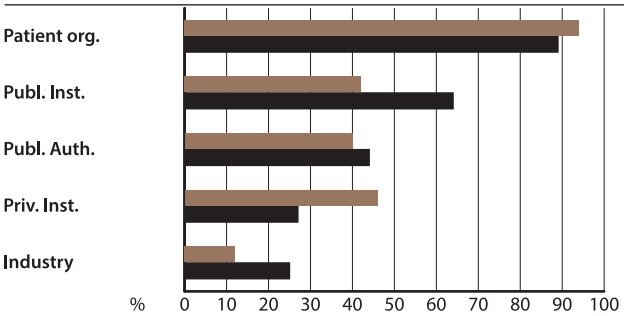
Amongst the 101 diseases represented by responses from Germany, the most represented include Idiopathic achalasia (57), Idiopathic panuveitis (53), Rett syndrome (39), Familial spastic paraplegia (23), Williams syndrome (19), Idiopathic acute transverse myelitis (15), Scleroderma (15), Systemic lupus erythematosus (15),



AIMS OF A REGISTRY

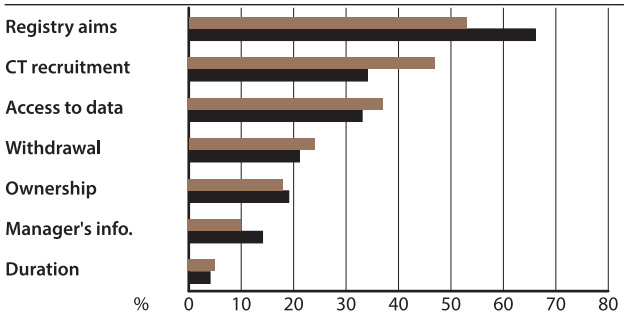
German respondents much less frequently reported a preference for healthcare and social services planning (18.5%) as an important registry aim as compared to most other respondents.

«For rare diseases, the register should always have a patient part, for «soft» data, observations that seem important for the individuals themselves.»



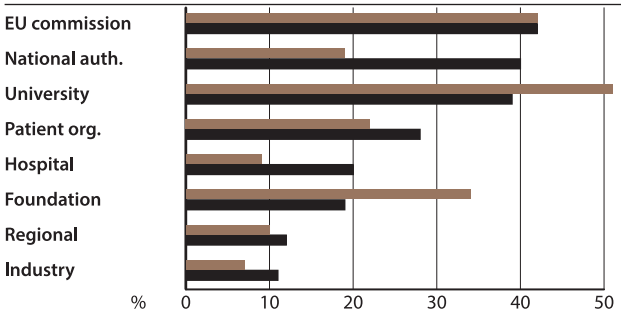
REGISTRY USERS/ACCESS

German respondents were particularly favourable for patient organisations (94.1%) to have access to registry data. As compared to other European responde nts, more German respondents favoured the access to data for private citizens and institutions (45.5%).



INFORMATION COMMUNICATED UPON ENROLMENT IN A REGISTRY

German respondents did not differ in the overall ranking of the types of information communicated to patients participating in registries. However, the preference for information on the possibility of being contacted for clinical trials (47.0%) was most significantly observed amongst German respondents as compared to respondents from any other country.



LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY

German respondents most frequently favoured universities and research institutes (51.2%) in assuring the long-term financial sustainability of a registry. Unlike most other countries, these respondents did not frequently favour national authorities (18.6%) or hospitals (9.3%) a source of long-term sustainability for a registry.

GREECE

Regional registries	0
National registries	2
European registries	0
Global registries	0
Total number of registries	2

GREEK REGISTRIES LANDSCAPE

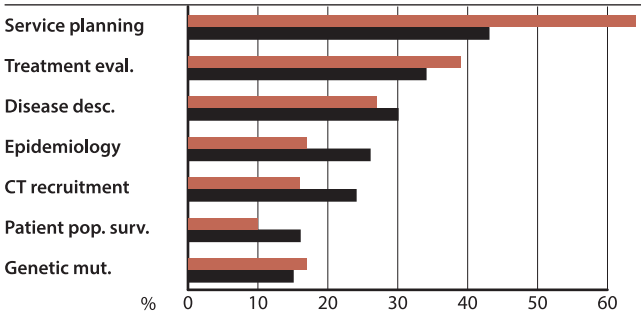
There is currently no national registry for all RD in Greece. One of the main tasks of the Greek Center for Disease Control and Protection (KEELPNO) and the new steering committee for RD is to set up a national registry in compliance with international standards.
A pilot registry that started in 2011 is currently in progress and creation of a registry of RD registries was discussed at the second Europlan conference.
In the absence of a national registry for RD or national funding, scientific societies covering RD appointed working groups which, in collaboration with respective centres of expertise and patients organisations, have created registries for several RD. Greek registries contribute to the European registries EUROCARE CF, EIMD and RD Connect.

PARTICIPANTS IN THE SURVEY

A total of 159 respondents were from Greece representing 4.6% of total survey responses. This represents a moderate group of respondents per country. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Greece are presented. For the remainder of survey questions, Greek respondents did not differ significantly in their response as compared to respondents from other countries.
The ratio of responses per million Greek inhabitants is relatively high (14.1) suggesting that responses from Greece somewhat strongly represent the overall opinion of Greek citizens. Amongst the 49 diseases represented by responses from Greece, the most represented include Crohn's disease (24), Cystic fibrosis (18), Tuberous sclerosis (18), Neurofibromatosis type 1 (12), Beta-thalassemia (8), systemic lupus erythematosus (7), Gaucher disease (6) and Rett syndrome (6).

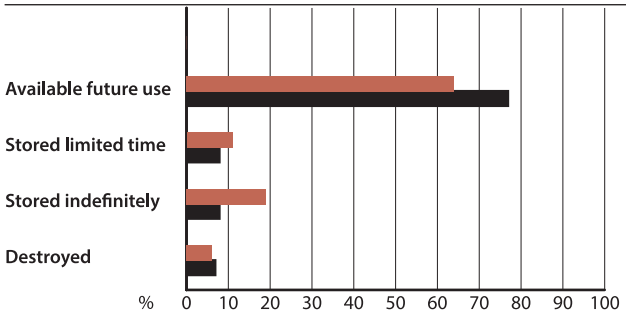
« Incentives need to be given for research on our diseases in the case that treatments may be discovered so that we can finally be cured. However, it seems that we are too few and that it isn't in the interest of the pharmaceutical industry to deal with us... »

AIMS OF A REGISTRY



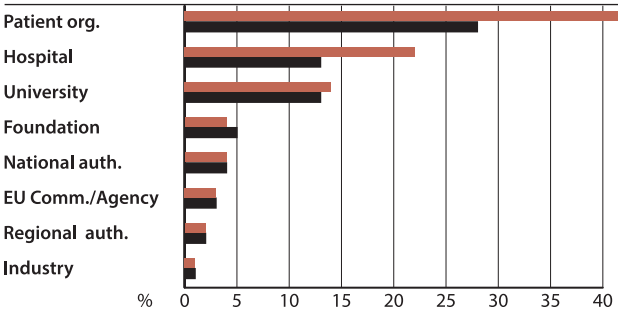
Greek respondents even more frequently reported a preference for healthcare and social services planning (63.7%) as an important registry aim as compared to most other respondents.

REGISTRY CLOSURE



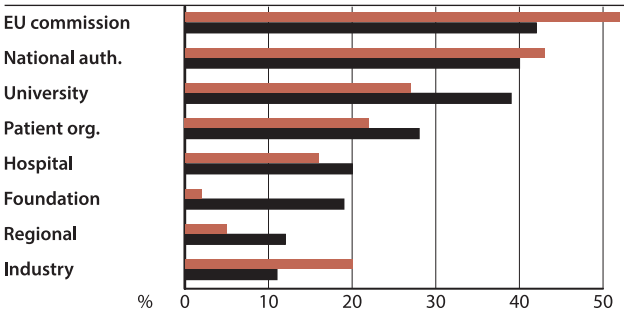
Greek responses reflected a less frequent preference (63.6%) to make data available to other registries or the research community and more frequently preferred data to be stored for an indefinite time (19.2%) upon a registry's closure as compared to most other countries.

INITIATIVE FOR ESTABLISHING A REGISTRY



Greek respondents that knew of the existence of a registry for their disease, very frequently reported patient organisations (51.1%) as the initiator.

LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY



Greek respondents aware of the existence of a registry for their disease, very frequently (52.0%) favoured the European Commission/EU Agency in assuring the long-term financial sustainability of a registry. These respondents less frequently favoured foundations (1.8%) and more frequently favoured industry (19.7%) a source of long-term sustainability as compared to other countries.

HUNGARY

Regional registries	0
National registries	3
European registries	0
Global registries	0
Total number of registries	3

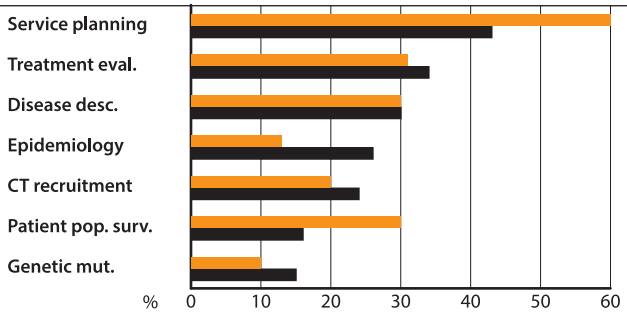
«It would be very important to delineate, in a common European legal framework for rare disease registries, what is the goal of the registers, who can use them and for what purpose.»

HUNGARY REGISTRIES LANDSCAPE

Although Hungarian clinical centres for RD maintain hospital-based registries, RD cases are not reported to a national data collecting system. And collection standards are based on local needs for care management and research requirements. The National Rare Disease Center has initiated the establishment of an overall registry for RD.
The National Registry of Congenital Anomalies (VRONY) currently operates countrywide according to the EUROCAT protocol. Hungary also contributes to European Registries such as TREAT-NMD, EUROCAT, SCNIR and EUROCARE CF.

PARTICIPANTS IN THE SURVEY

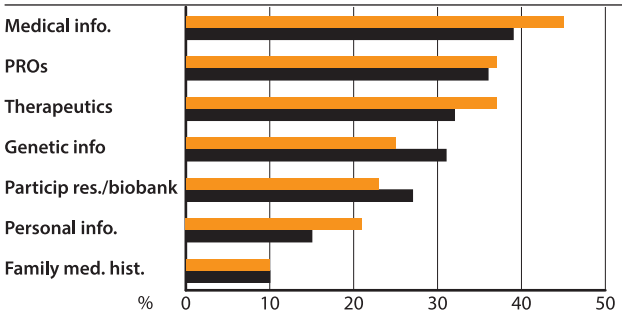
A total of 99 survey respondents were from Hungary representing 2.8% of total survey responses. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Hungary are presented. For the remainder of survey questions, Hungarian respondents did not differ significantly in their responses as compared to the general survey results.
The ratio of responses per million Hungarian inhabitants is moderately high (9.9) suggesting that responses from Hungary may somewhat represent the overall opinion of Hungarian citizens living with RD. Of the 46 disease groups that responded to the survey from Hungary, the most represented diseases were Williams syndrome (10), Esophageal atresia (8), MELAS syndrome (8), Fragile X syndrome (6), Neurofibromatosis (6), Smith-Lemli-Opitz syndrome (4) and Tetralogy of Fallot (4).



AIMS OF A REGISTRY

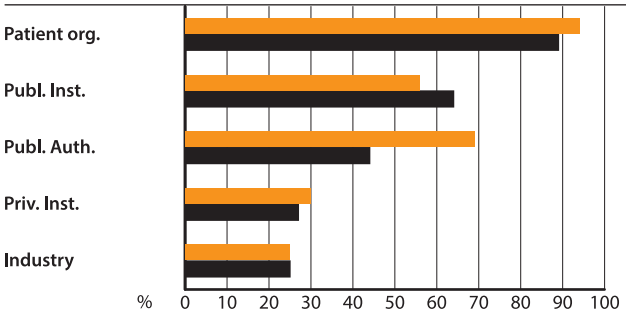
Hungarian respondents even more frequently reported a preference for healthcare and social services planning (59.6%) as an important registry aim as compared to other respondents.

TYPES OF INFORMATION COLLECTED IN A REGISTRY



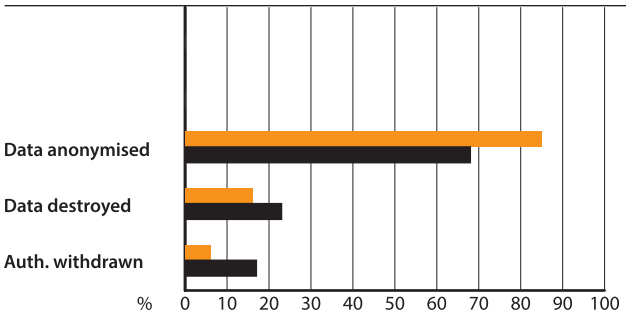
Hungarian respondents communicated the importance of medical information (44.6%), therapeutic use (37.5%) and personal information (21.1%) more frequently than most other respondents.

REGISTRY USERS/ACCESS



Hungarian respondents very frequently expressed a preference for patient organisations (93.6%) and public authorities (69.1%) to have access to registry data.

WITHDRAWAL FROM A REGISTRY



Hungarian respondents reported a preference for anonymising their data for future research following the withdrawal from a registry even more frequently (85.1%) than respondents from other countries.

COMMON EUROPEAN REGISTRY INFRASTRUCTURE

Hungarian respondents, more than overall respondents, most strongly agreed (94.4%) with the establishment of a common portal by the European Commission and Member States for all RDPR in Europe. A few respondents had no opinion (2.3%) or disagreed (3.4%).

ITALY

Regional registries	7
National registries	46
European registries	3
Global registries	7
Total number of registries	63

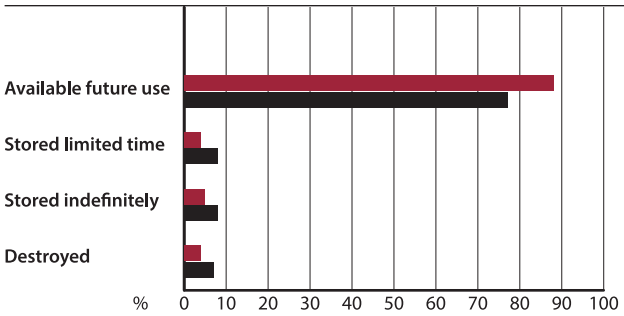
ITALIAN REGISTRIES LANDSCAPE

The Italian National Registry for Rare Diseases was established at the National Center for Rare Diseases in the Instituto Superiori di Sanità (CNMR– ISS) in 2001. Its objectives include epidemiological surveillance and national and regional planning of health measures for RD patients as well as support for scientific research in the clinical, biomedical fields. The National Registry collects the data coming from Regional registries. Since the creation of this national registry each Italian region has established its own RDPR sending data collected in accredited expert centres for RD using a common data set. Interregional registries have also been established. The National Registry is linked to the regional, interregional and international registries such as EUROCAT, EIMD, EURO-WABB, EuroWilson, TREAT-NMD, HAE-registry, RBDD, AIR, EUROCARE-CF and RD Connect.

PARTICIPANTS IN THE SURVEY

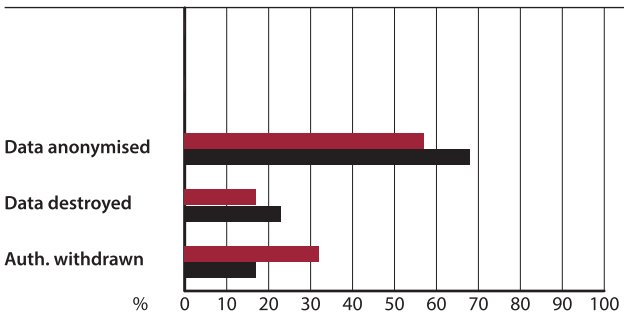
A total of 715 survey respondents were from Italy representing 20.6% of total survey responses. This represents the second largest group of respondents per country.
As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Italy are presented.
For the remainder of survey questions, Italian respondents did not differ significantly in their response as compared to respondents from other countries.
Amongst the 225 diseases represented by responses from Italy, the most represented include Idiopathic steroid-sensitive nephrotic syndrome (39), Duchenne muscular dystrophy (36), Behcet disease (31), Williams syndrome (30), Dravet syndrome (25), Achondroplasia (16), Essential thrombocythemia (16) and Familial mediterranean fever (15),

«I wish there was a synergy between all the existing structures worldwide. Genetic diseases have global importance. In Italy we have too many differences in the transposition of directives and in the use of research funds from region to region.»



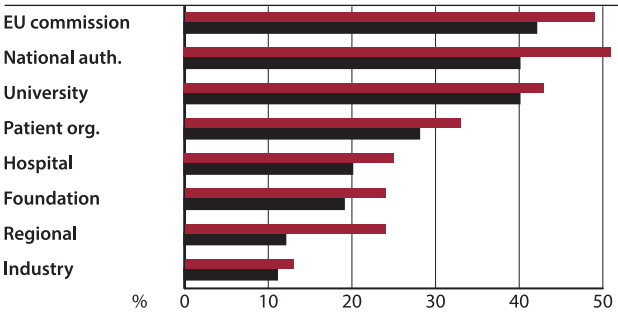
REGISTRY CLOSURE

Italian responses reflected an even stronger preference (87.9%) for making data available to other registries or the research community upon a registry's closure as compared to most other countries. Very few Italian respondents reported the choice to destroy their data, store it indefinitely or store it for a limited time.



WITHDRAWAL FROM A REGISTRY

Although the majority of Italian respondents reported a preference for anonymising their data for future research following the withdrawal from a registry, they did so less frequently (57.1%) than respondents from other countries. Italian respondents more frequently reported a preference for withdrawing authorisation for future use of data (32.2%) than other countries.



LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY

Italian respondents much more frequently favoured regional authorities (24.0%) and somewhat more frequently national authorities (51.5%) in assuring the long-term financial sustainability of a registry.

PORTUGAL

Regional registries	1
National registries	11
European registries	0
Global registries	0
Total number of registries	12

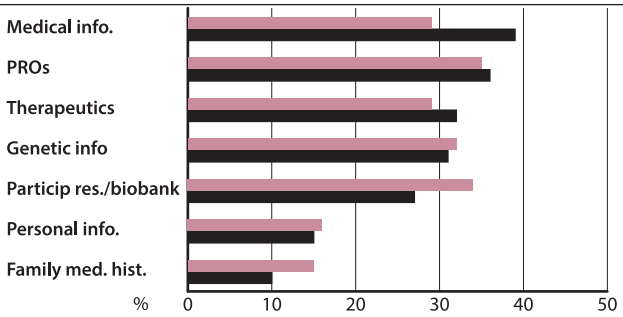
PORTUGUESE REGISTRIES LANDSCAPE

Several regional and national-level RDPR are currently available in Portugal, most publicly supported and a few from private institutions. The National Institute of Health operates several registries accounting for RD patients: National Commission for the Portuguese Registry of Paramyloidosis, National Commission for Lysosomal Storage Diseases, National Registry of Congenital Anomalies (RENAC) and National Newborn Screening Commission. Upon their own initiative, many patients are also included in international registries. Portuguese institutions also participate, or have participated, in European registries, such as, E-IMD, TREAT-NMD, EUROCARE CF, EUROCAT, EBAR, SCNIR, CHS, SPATAX, EUROWILSON and RD Connect.

PARTICIPANTS IN THE SURVEY

A total of 148 survey respondents were from Portugal representing 4.3% of total survey responses. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Portugal are presented. For the remainder of survey questions, Portuguese respondents did not differ significantly in their responses as compared to the general survey results.

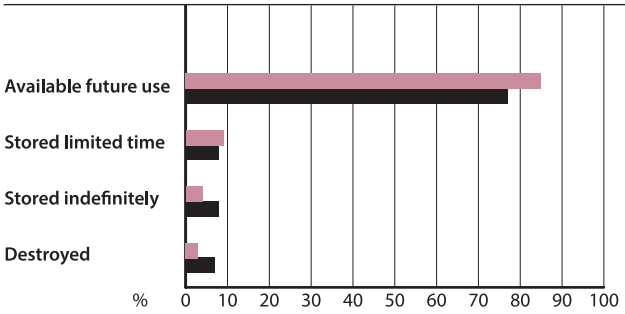
Among the 60 diseases included in Portuguese responses, the most represented were Behcet syndrome (35), Retinitis pigmentosa (12), epilepsy (10), Stargardt disease (6), Friedreich ataxia (5), Machado-Joseph disease type 1 (5) and Phenylketonuria (4).



TYPES OF INFORMATION COLLECTED IN A REGISTRY

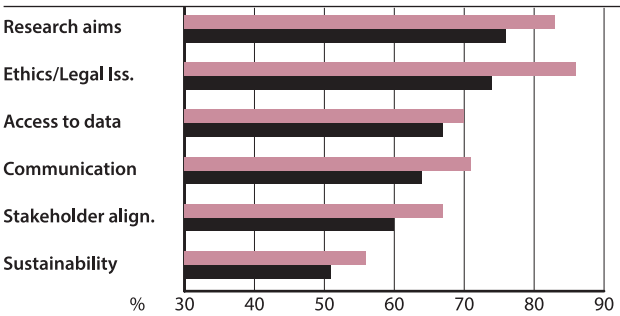
Portuguese respondents communicated the importance of collecting medical information (29.5%) much less frequently than other respondents and more frequently communicated the importance of patient participation in clinical research or a biobank (34.0%).

REGISTRY CLOSURE



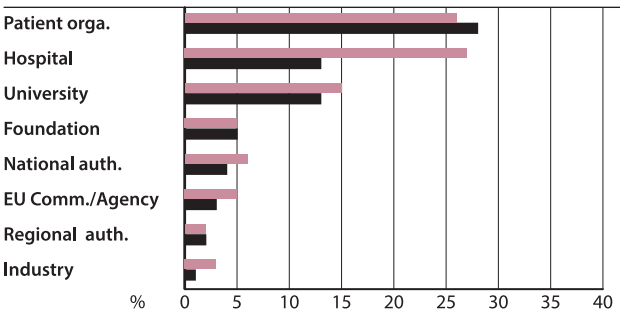
Portuguese responses reflected an even strong preference (85.1%) to make data available to other registries or the research community upon a registry's closure as compared to most other countries. Very few Portuguese respondents reported the choice to destroy their data, store it indefinitely or store it for a limited time.

REGISTRY GOVERNANCE



Overall, Portuguese respondents more frequently reported the importance of a patient perspective in the governance of a registry as compared to other respondents – especially for aspects such as ethical and legal issues (83.2%) and research aims (86.1%).

INITIATIVE FOR ESTABLISHING A REGISTRY



Portuguese respondents more frequently reported hospitals (26.9%) as the initiators of a registry as compared to other countries.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

Portuguese respondents, even more than overall respondents, strongly agreed (92.9%) with the proposal of a European legislation to uniformly regulate RDPR across Europe. A few respondents had no opinion (5.5%) and even less disagreed (1.6%).

«The registry can be of huge scientific, social and economic utility. But it can not and must not serve to violate the privacy or dignity of people affected by rare diseases. In my opinion, this is a fundamental aspect for the creation of registries. I understand that it may be important to have an inventory of rare diseases and patients to get a better understanding of the disease and to improve their conditions of life, their health and their social, economic and institutional support.»

ROMANIA

Regional registries	0
National registries	9
European registries	0
Global registries	0
Total number of registries	9

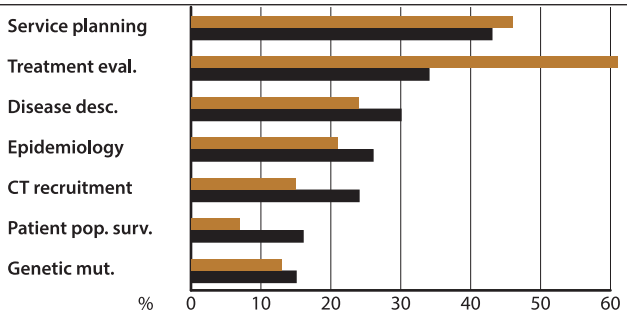
«I think that there is a need to establish a recommendation for the establishment of rare disease registries in countries where they do not exist, for the most «common» rare diseases.»

ROMANIAN REGISTRIES LANDSCAPE

There are currently several national RDPR in Romania with several others in development. An official decision of the Romanian Government of 26 March 2008 stipulates that National Registries should be established and maintained for cardio-vascular diseases (including congenital anomalies), cancers, diabetes mellitus, haemophilia, thalassaemia, psychiatric diseases as well as a National Registry for RD. Since then the Romanian National Plan for Rare Diseases has proposed a common RDPR for epidemiological and/or clinical research based on databases in each centre of expertise. The deadline for this initiative is 2013.
Romania contributes to the following European registries: EBAR, EUROCARE-CF and EUTOS.

PARTICIPANTS IN THE SURVEY

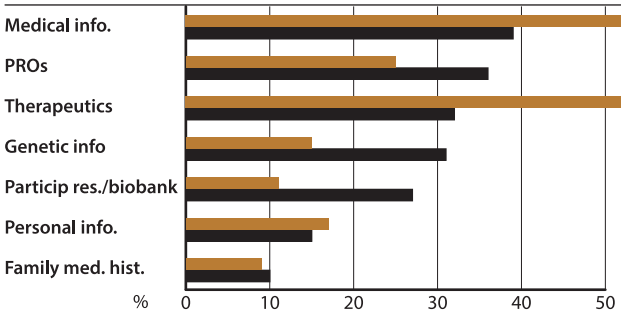
A total of 46 survey respondents were from Romania representing 1.3% of total survey responses. This represents the second smallest group of respondents per country.
As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Romania are presented. For the remainder of survey questions, Romanian respondents did not differ significantly in their response as compared to respondents from other countries.
Among the 15 diseases included in Romania responses, the most represented were Myasthenia gravis (26), Osteogenesis imperfecta (6), Dravet syndrome (2), Williams syndrome (2), Acute intermittent porphyria (1), Autism (1), Beta-thalassemia (1) and Camurati-Engelmann disease (1).



AIMS OF A REGISTRY

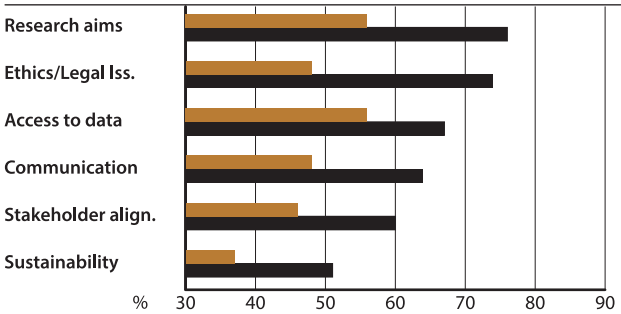
Romanian respondents more frequently reported a preference for treatment evaluation (60.9%) as an important registry aim as compared to other respondents.

TYPES OF INFORMATION COLLECTED IN A REGISTRY



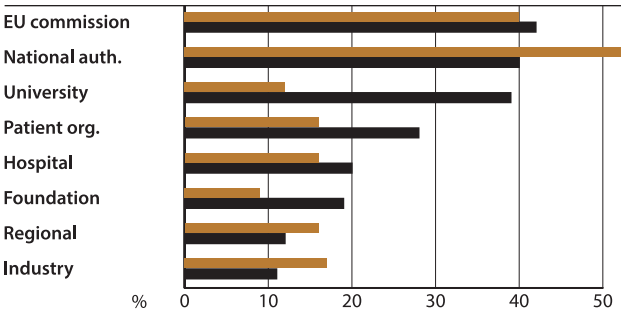
Romanian respondents communicated the importance of medical information (59.3%) and therapeutic use (54.1%) more frequently than most other respondents. ommoloreiusvolenis nonet moluptatus.

REGISTRY GOVERNANCE



Overall, Romanian respondents much less frequently reported the importance of a patient perspective in all aspects of governance of a registry as compared to other respondents.

LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY



Romanian respondents were particularly less frequently in favour of universities and patient organisations (15.5%) and significantly more frequently in favour of national authorities (63.6%) in assuring the long-term financial sustainability of a registry.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

Romanian respondents, even more than overall respondents, strongly agreed (95.3%) with the proposal of a European legislation to uniformly regulate RDPR across Europe. A few respondents had no opinion (2.3%) or disagreed (2.3%).

«It is extremely urgent to establish national registries for rare diseases in the whole European Union. Information about rare diseases is very scarce and the existence of registries would fill this void.»

SPAIN

Regional registries	4
National registries	33
European registries	2
Global registries	0
Total number of registries	39

SPANISH REGISTRIES LANDSCAPE

To respond to limitations in data collection the Institute of Health Carlos III (ISCIII) financed the Spanish Rare Diseases Registries Research Network (SpainRDR) coordinated by the Institute of Rare Diseases Research (IIER) until December 2014 to further develop this platform. SpainRDR aims to create a central platform providing access to data from three of sources: regional population-based registries, disease registries, and patient-reported data (personal data and diagnosis). On the international side Spanish health professionals participate in several European and international networks including: EUROCAT, ERCUSYN, EUGINDATPIADATABASE, EIMD, ESID, EURO-WABB, MOLDIAG-PACA, AIR, SCNIR, EUROCARE CF, ENERCA, TREAT-NMD and RD Connect.

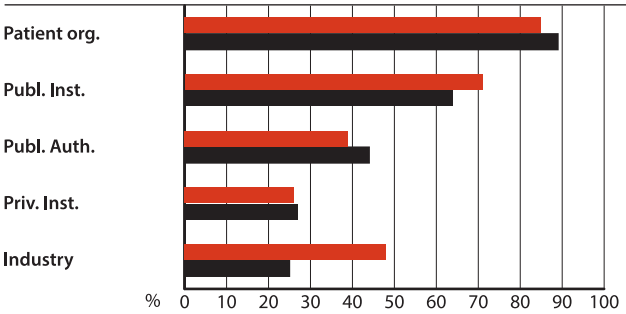
PARTICIPANTS IN THE SURVEY

A total of 865 survey respondents were from Spain representing 25% of total survey responses. This represents the largest group of respondents per country. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to Spain are presented. For the remainder of survey questions, Spanish respondents did not differ significantly in their response as compared to respondents from other countries.

Amongst the 248 diseases represented by responses from Spain, the most represented include Scleroderma (38), Cystic fibrosis (35), Ehlers-Danlos syndrome (28), Lymphangioleiomyomatosis (25), Barrett esophagus (23), Duchenne muscular dystrophy (23) and Epidermolytic epidermolysis bullosa (23), Hereditary angioedema (21), Williams syndrome (19), Tuberous sclerosis (17), Charcot-Marie-Tooth disease (17), Fragile X syndrome (16), Bladder exstrophy (13), Prader-Willi syndrome (13) and Steinert myotonic dystrophy (13).

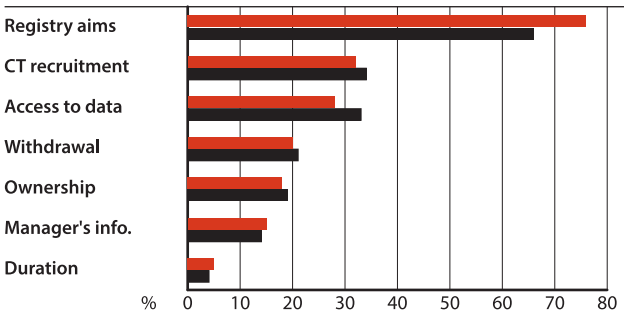
« My doctor has not been able to confirm for me if I have been registered in the rare disease registry portal, because another doctor did it (...). I think you should always inform a patient that he/she has been registered (...). Although it is important to regulate who and what data can be accessed depending on the purpose for which it is needed, it is also important to share information and inform stakeholders of developments or advances. »

REGISTRY USERS/ACCESS



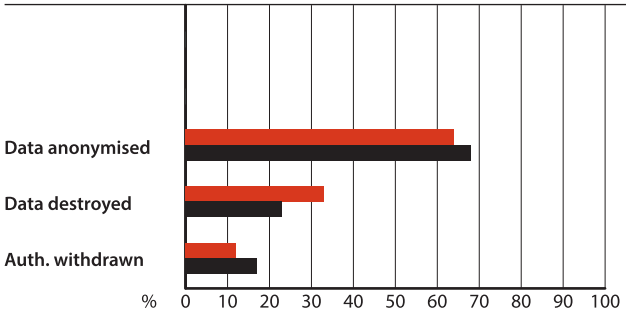
Like the majority of respondents, Spanish respondents most frequently expressed a preference for patient organisations (85%) and public institutions (71%) to have access to registry data. As compared to other European respondents, many more Spanish respondents favoured the access to data for industry (48.1%).

INFORMATION COMMUNICATED TO PATIENT UPON ENROLMENT IN A REGISTRY



Spanish respondents did not differ in the overall ranking of the types of information communicated to patients participating in registries. However, the preference for information on the registry's aim (76.0%) was most significantly observed amongst Spanish respondents as compared to respondents from any other country.

WITHDRAWAL FROM A REGISTER



Although the majority of Spanish respondents did communicate a preference for anonymising their data for future research following the withdrawal from a registry, they did so less frequently (64.3%) than respondents from other countries. Spanish respondents more frequently reported a preference for having data destroyed (32.7%).

COMMON EUROPEAN REGISTRY INFRASTRUCTURE

Spanish respondents, even more than overall respondents, strongly agreed (94.2%) with the establishment of a common portal European Commission and Member States for all RDPR in Europe. A few respondents had no opinion (5.2%), but almost none (0.6%) disagreed (Figure 4).

UNITED KINGDOM

Regional registries	13
National registries	45
European registries	7
Global registries	5
Total number of registries	70

UNITED KINGDOM REGISTRIES LANDSCAPE

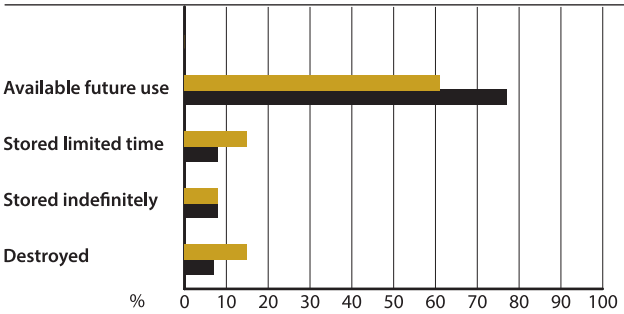
A number of regional and national registries exist in the UK for specific and groups of RD though they are not centralised in any way. A recent initiative, the Clinical Practice Research Datalink (CPRD), supported by the National Health Service (NHS), jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA) allows access to anonymised patient data for observational studies potentially helping those interested in RD to advance knowledge and understanding of rare conditions. The United Kingdom contributes to the following European registries: EUROCAT, EIMD, TREAT-NMD, AIR, EUROCARE-CF, EURO-WABB, EUHASS, EUROPAC, SCNIR, European Prader-Willi database, EUROWILSON and RD Connect.

PARTICIPANTS IN THE SURVEY

A total of 111 survey respondents were from the United Kingdom representing 3.2% of total survey responses. As the results below highlight only the differences in responses per country as compared to other countries in Europe, only a few results specific to the United Kingdom are presented. For the remainder of survey questions, United Kingdom respondents did not differ significantly in their responses as compared to the general survey results. The ratio of responses per million United Kingdom inhabitants is low (1.8) suggesting that responses from the United Kingdom may not represent the opinion of all United Kingdom citizens living with RD. Amongst the 38 diseases represented by responses from the United Kingdom, the most represented include Beta-thalassemia (33), Relapsing polychondritis (12), Epidermolytic epidermolysis bullosa (6), Behcet disease (5), Alkaptonuria (4), Alternating hemiplegia of childhood (3) and Birdshot chorioretinopathy (3).

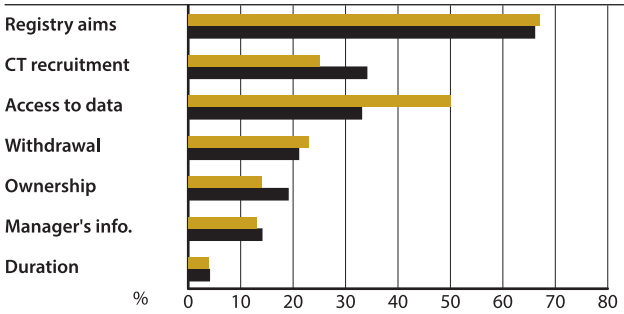
« The importance of registers cannnot be underestimated. Our patient-led register was instrumental in triggering a national, confidential enquiry into the causes of deaths of patients. When this was linked to epidemiological and survivability data it lead to the setup of a national screening programme; it also monitored the uptake of prenatal screening. »

REGISTRY CLOSURE



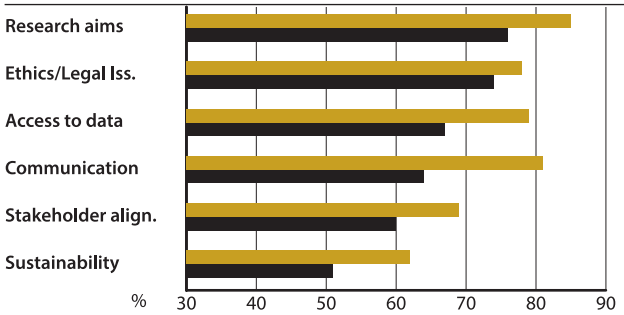
United Kingdom responses reflected a less frequent preference (61.6%) to make data available to other registries or the research community and more frequently preferred data to be stored for a limited time (15.2%) or destroyed (15.2%) upon a registry's closure as compared to most other countries.

INFORMATION COMMUNICATED UPON ENROLMENT IN A REGISTRY



United Kingdom respondents differed in the overall ranking of the types of information communicated to patients upon enrolment in a registry.
The preference for information about access to data (50.4%) was most significantly observed amongst United Kingdom respondents as compared to respondents from any other country.

REGISTRY GOVERNANCE



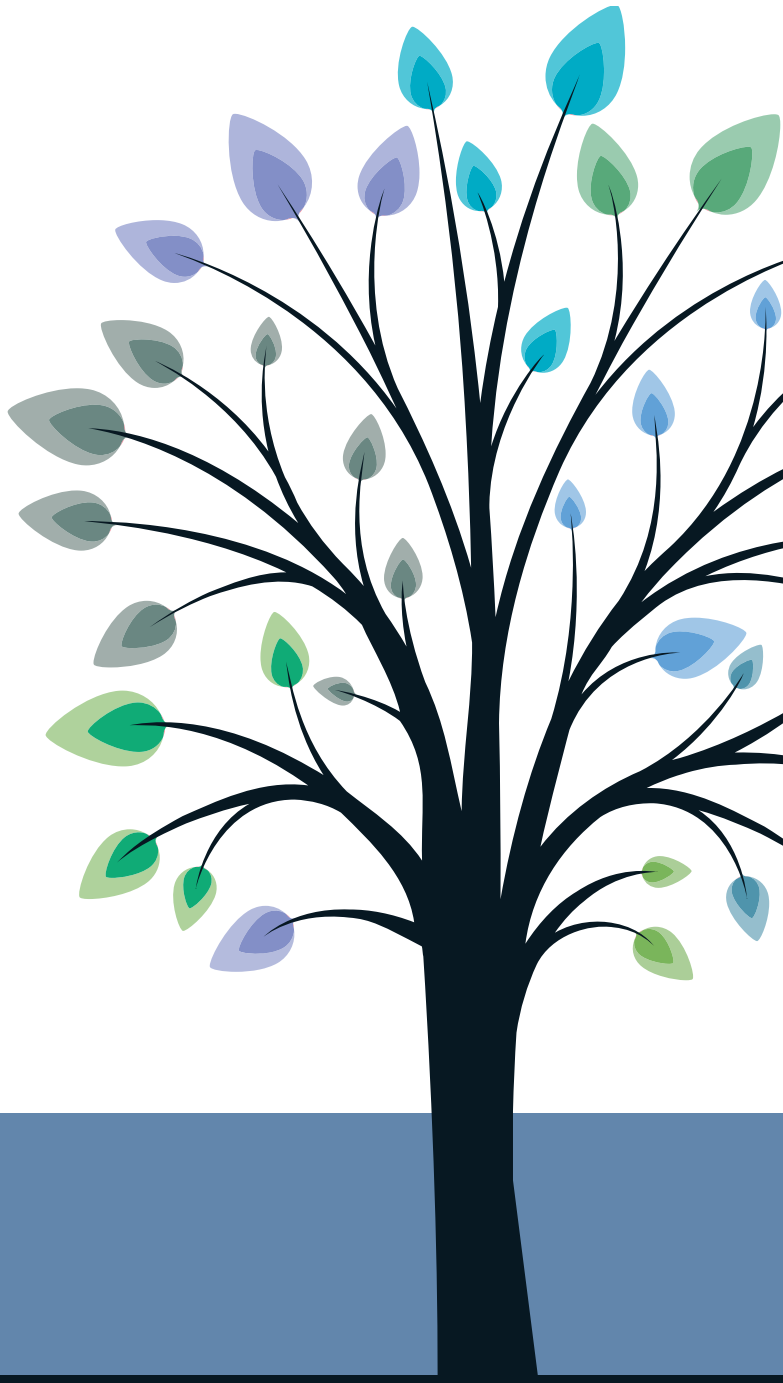
Overall, United Kingdom respondents more frequently reported the importance of a patient perspective in the governance of a registry as compared to other respondents – especially for aspects such as research aims (85.1%), communication with users (80.7%), access to data (79.1%) and information about the registry's sustainability/closure (62.5%).

GBR
ALL

COMMON EUROPEAN REGISTRY INFRASTRUCTURE

United Kingdom respondents agreed less frequently than overall respondents (78.6%) with the establishment of a common European Commission and Member States portal for all RDPR in Europe. A significant number had no opinion (15.5%) and a few (5.9%) disagreed.

RESULTS BY DISEASE



BEHÇET'S SYNDROME

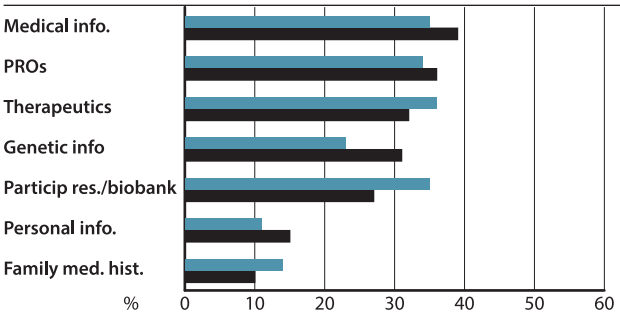
CLINICAL PICTURE

Behçet's syndrome (BS) is a chronic, relapsing, multisystemic vasculitis characterized by mucocutaneous lesions, as well as articular, vascular, ocular and central nervous system manifestations. The disease is characterized by ulcers affecting the mouth and genitals, various skin lesions, and abnormalities affecting the eyes. Although it can happen at any age, symptoms generally begin when individuals are in their 20s or 30s. BS is most often reported in populations along the Silk Road, with highest prevalence reported in Turkey. European cases are more often described in Mediterranean countries. The exact cause of Behcet's syndrome is unknown. In the absence of treatment, the prognosis is severe due to ocular involvement leading potentially to blindness, the risk of lethal arterial rupture and neurological symptoms potentially causing encephalopathy that may lead to a loss of autonomy. Although there is no cure for BS, people can usually control symptoms with proper medication, rest, exercise, and a healthy lifestyle.
The goal of treatment is to reduce discomfort and prevent serious complications such as disability from arthritis or blindness. Intensive ophthalmological care coupled with immunosuppressive treatment has been shown to reduce morbidity greatly. The type of medicine and the length of treatment depend on the person's symptoms and their severity. It is likely that a combination of treatments will be needed to relieve specific symptoms.

Age of onset	
Prevalence	+
Genetic Nature (inheritance)	?
Number of Regional, National, European or International Registries	11

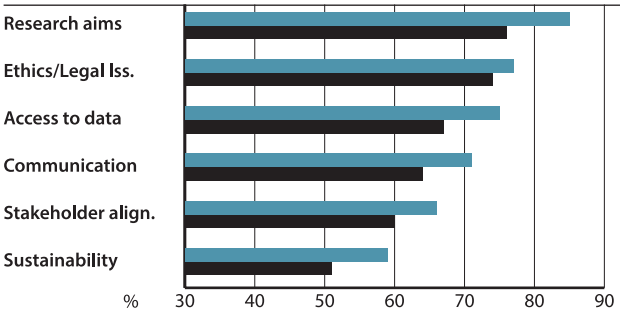
PARTICIPANTS IN THE SURVEY

The countries most represented amongst respondents concerned with BS include France (17), Italy (31) and Portugal (35).
A total of 112 survey participants reported being concerned with BS. The results below highlight major differences in opinion from BS respondents compared to other disease groups. As such, only a few results specific to BS are presented. For the remainder of survey questions, BS respondents did not differ significantly in their responses.



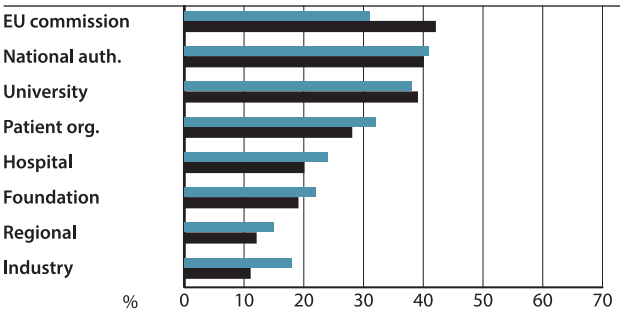
TYPES OF INFORMATION COLLECTED IN A REGISTRY

BS respondents communicated the importance of collecting information more frequently for patient participation in clinical research or a biobank (35.1%) and less frequently for personal information (11.4%) as compared to other respondents.



REGISTRY GOVERNANCE

Overall, BS respondents more frequently reported the importance of a patient perspective in the governance of a registry as compared to other respondents – especially for aspects such as research aims (85.4%) and access to data (74.7%).



LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY

BS respondents more frequently favoured patient organisations (32.3%), hospitals (24.2%) and industry (17.9%) in assuring the long-term financial sustainability of a registry as compared to other respondents. Only 31.2% favoured the European Commission/EU Agency in assuring this sustainability.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

BS respondents very frequently (91.6%) agreed with the proposal of a European legislation to uniformly regulate RDPR across Europe. A few respondents had no opinion (8.4%) and none disagreed.

CYSTIC FIBROSIS

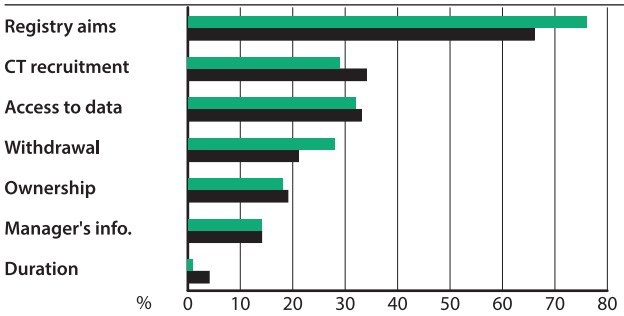
CLINICAL PICTURE

Cystic Fibrosis (CF) is an inherited genetic disease that affects the mucus glands of the lungs, liver, pancreas, and intestines, resulting in the production of thick sticky mucus.
The disease is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene on Chromosome 7. The thick mucus produced in people with CF can clog lungs, obstruct the pancreas and stop natural enzymes from helping the body break down and absorb food. As such, people with CF can have a variety of additional symptoms including very salty-tasting skin, persistent cough, lung infections, wheezing or shortness of breath, poor growth/weight gain, frequent, greasy, bulky stools or difficulty in bowel movements.
The disease is chronic and progressive causing progressive disability due to multi-organ failure. As such the lifespan of people with CF is shortened. Although the severity of the disease can vary greatly from person to person, nearly all patients with CF need to take daily medications, including inhalations, dietary supplements, and enzymes their entire lives to aid breathing and digestion.

Age of onset	
Prevalence	
Genetic Nature (inheritance)	
Number of Regional, National, European or International Registries	41

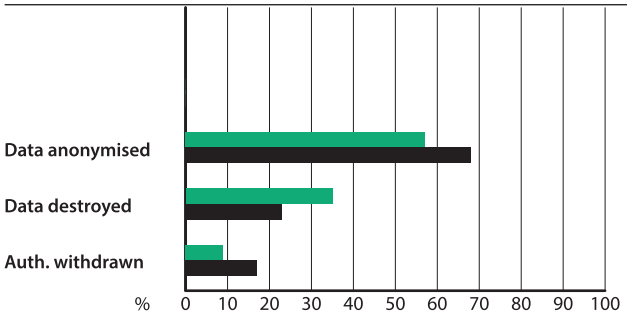
PARTICIPANTS IN THE SURVEY

The countries most represented amongst respondents concerned with CF include Spain (35) and Greece (18).
A total of 65 survey participants reported being concerned with CF. The results below highlight major differences in opinion from CF respondents compared to other disease groups. As such, only a few results specific to CF are presented. For the remainder of survey questions, CF respondents did not differ significantly in their responses.



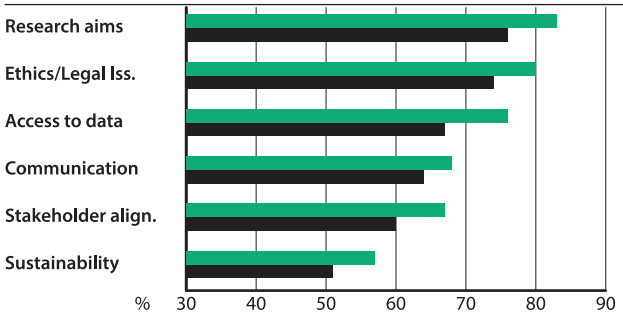
INFORMATION COMMUNICATED UPON ENROLMENT IN A REGISTRY

CF respondents similarly responded in the overall ranking of the types of information communicated to patients participating in registries. However, the preference for information about registry aims (75.7%) and withdrawal from the registry (28.3%) was more significantly observed amongst CF respondents as compared to others.



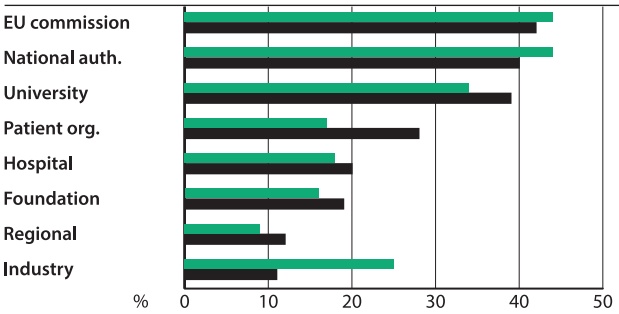
WITHDRAWAL FROM A REGISTRY

CF respondents less frequently reported a preference for anonymising their data for future research following the withdrawal from a registry (56.9%) and more frequently for having their data destroyed (34.5%) as compared to other respondents.



REGISTRY GOVERNANCE

Overall, CF respondents more frequently reported the importance of a patient perspective in the governance of a registry as compared to other respondents – especially for aspects such as research aims (83.0%), access to data (76.1%) and stakeholder alignment (67.3%)



LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY

CF respondents less frequently favoured patient organisations (17.0%) and more frequently favoured industry (24.8%) in assuring the long-term financial sustainability of a registry as compared to other respondents.

DUCHENNE MUSCULAR DYSTROPHY

Age of onset	
Prevalence	+
Genetic Nature (inheritance)	
Number of Regional, National, European or International Registries	11

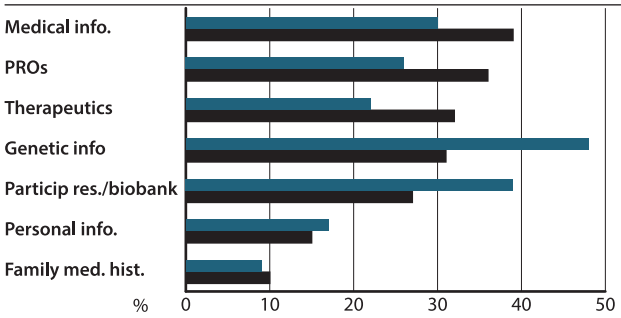
CLINICAL PICTURE

Duchenne muscular dystrophy (DMD) is a rapidly progressive form of muscular dystrophy that occurs primarily in boys. It is caused by a mutation in a gene, called the DMD gene, which encodes dystrophin, a protein that helps keep muscles intact. DMD is inherited in an X-linked recessive fashion; however, it may also occur in people from families without a known family history of the condition. Individuals who have DMD have progressive loss of muscle function and weakness, which begins in the lower limbs. In addition to the skeletal muscles used for movement, DMD may also affect the muscles of the heart.
DMD symptoms usually begin in childhood and progress severely, eventually affecting all voluntary muscles as well as involuntary muscles such as the heart and breathing muscles. Most boys with DMD have normal intelligence, but some have learning or behavioural difficulties. Women can be carriers of DMD, but usually do not exhibit symptoms, except for a small numbers of "manifesting carriers" experiencing mild symptoms. There is no known cure for DMD, but the disease is the subject of many research projects and clinical trials in drug and gene therapies. Life expectancy has increased during the last decades thanks to optimal management methods. However, due to cardiac or other complications, life can be significantly shortened in patients with DMD. Symptomatic treatments, including orthopaedic, respiratory and cardiac therapies, help with many complications and help maximizing the quality of life.

PARTICIPANTS IN THE SURVEY

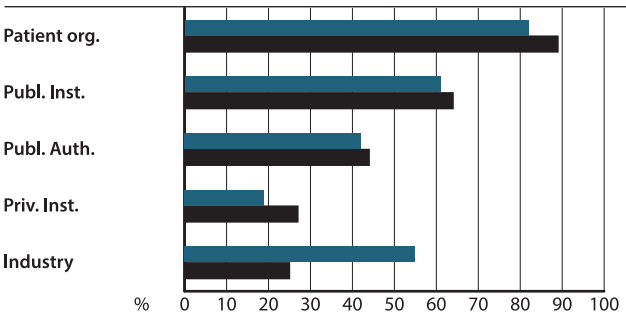
The countries most represented amongst respondents concerned with DMD include Italy (36) and Spain (23).
A total of 67 survey participants reported being concerned with DMD. The results below highlight major differences in opinion from DMD respondents compared to other disease groups. As such, only a few results specific to DMD are presented. For the remainder of survey questions, DMD respondents did not differ significantly in their responses.

TYPES OF INFORMATION COLLECTED IN A REGISTRY



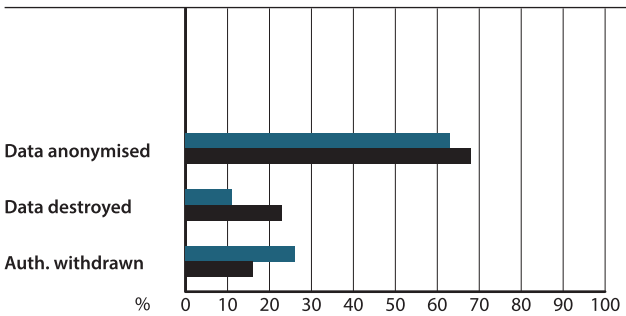
DMD respondents communicated the importance of collecting genetic information (48.2%) and patient participation in research or a biobank (39.5%) more frequently than most other respondents.

REGISTRY USERS/ACCESS



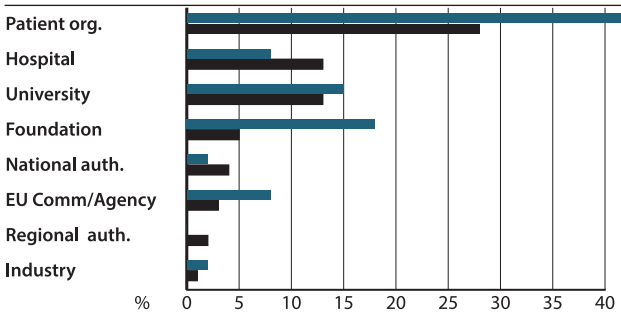
DMD respondents more frequently expressed a significantly more frequent preference for industry (55.2%) to have access to registry data as compared to other respondents.

WITHDRAWAL FROM A REGISTRY



Although most DMD respondents reported a preference for anonymising their data for future research (25.8%) following the withdrawal from a registry, a large percentage favoured withdrawing authorisation for further use of data (25.8%) upon withdrawal from a registry as compared to most other respondents.

INITIATIVE FOR ESTABLISHING A REGISTRY



DMD respondents that knew of the existence of a registry for their disease, more frequently reported patient organisations (64.5%) and foundations (17.8%) and less frequently reported hospitals (8.1%) as the initiator of a registry as compared to other respondents.

EHLERS-DANLOS SYNDROME

Age of onset	
Prevalence	
Genetic Nature (inheritance)	XX XX XY
Number of Regional, National, European or International Registries	11

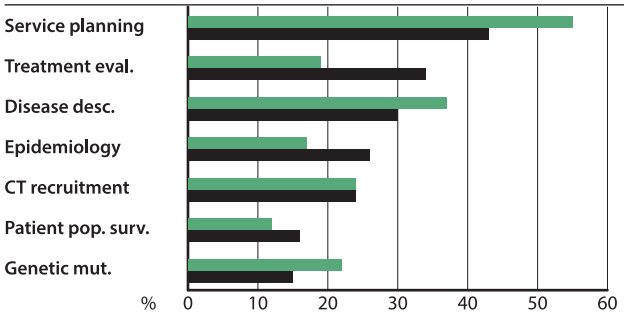
CLINICAL PICTURE

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of hereditary connective tissue diseases, caused by a mutation leading to the body's inability to produce collagen and characterized by joint hyperlaxity, cutaneous hyperelasticity and tissue fragility. There are several subtypes of EDS and symptoms vary widely depending on the type. The classic forms (former EDS types I and II) are characterised by the following major clinical diagnostic criteria: hyperextensible skin, atrophic cutaneous scars due to tissue fragility and joint hyperlaxity. Other minor manifestations include molluscoid tumors, subcutaneous spheroids, joint (sub)luxations, muscule hypotonia, and a family history of the disease. Symptoms that occur in rarer forms of EDS include pulmonary problems and high risk of blood vessel or organ rupture (vascular type, formerly EDS IV); congenital hip dislocation (arthrochalasia type, formerly EDS VIIB); serious eye conditions (kyphoscoliosis type, formerly EDS VI) and problems with blood clotting. Prognosis for people with EDS depends largely upon the type of EDS. Most individuals with EDS will have a normal lifespan, however, this is shortened in those with vascular type EDS. Treatment includes the management of symptoms and the prevention of further complications, through physiotherapy and the use of pain relievers and devices that support the musculoskeletal system. Symptoms usually appear in childhood but can onset later as well.
Chronic pain, if not correctly controlled, can lead to stress and depression. Serious injuries can also contribute to patients' anxiety. Patients with EDS may also experience extreme frustration with the fact that, although it is a debilitating condition, EDS symptoms are not necessarily visible to family, friends, colleagues and doctors, who insist that what a patient is feeling is "all in their mind".

PARTICIPANTS IN THE SURVEY

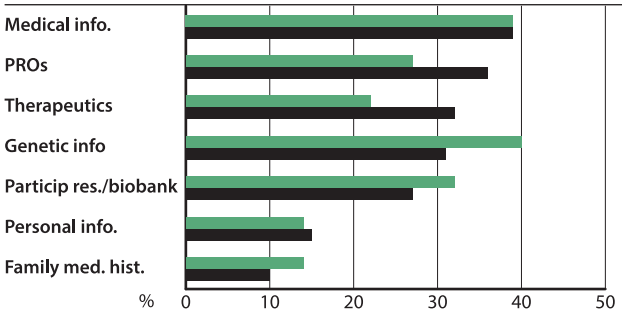
The countries most represented amongst respondents concerned with EDS include Spain (28) and Italy (11).
A total of 54 survey participants reported being concerned with EDS. The results below highlight major differences in opinion from EDS respondents compared to other disease groups. As such, only a few results specific to EDS are presented. For the remainder of survey questions, EDS respondents did not differ significantly in their responses.

AIMS OF A REGISTRY



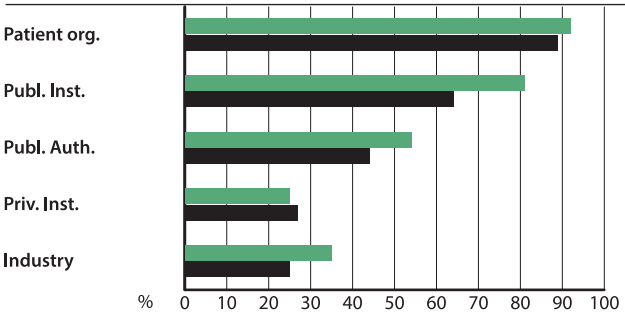
EDS respondents less frequently reported a preference for treatment evaluation (18.6%) and epidemiological aims (16.7%) as important registry aims as compared to other respondents. Rather, EDS respondents more frequently favoured service planning (55.1%), disease description (37.2%) and genetic mutations (21.8%) as compared to other respondents.

TYPES OF INFORMATION COLLECTED IN A REGISTRY



EDS respondents communicated the importance of collecting genetic information (40.1%) more frequently and patient reported outcomes (27.2%) and therapeutic use (22.5%) less frequently than most other respondents.

REGISTRY USERS/ACCESS



EDS respondents very frequently expressed a preference for patient organisations (92.3%) and public institutions (80.8%) to have access to registry data. As compared to other respondents, more EDS respondents (34.6%) favoured the access to data for industry.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

EDS respondents agreed even frequently than overall respondents (91.3%) with the proposal of a European legislation to uniformly regulate RDPR across Europe.

HEREDITARY SPASTIC PARAPALEGIA

Age of onset	
Prevalence	+
Genetic Nature (inheritance)	XX XX XY
Number of Regional, National, European or International Registries	0

CLINICAL PICTURE

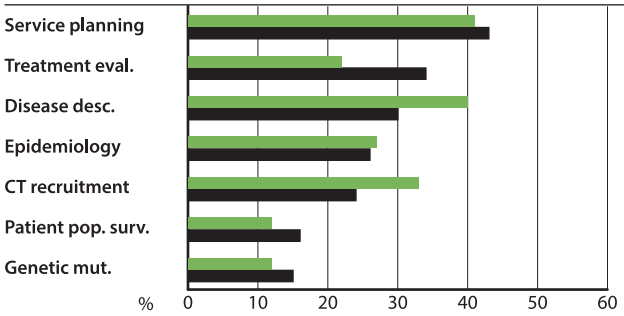
Hereditary spastic paraplegias (HSP) comprise a genetically and clinically heterogeneous group of rare, inherited neurodegenerative disorders characterized by progressive spasticity and hyperreflexia of the lower limbs. Researchers estimate that some 30 different types of HSP exist; the genetic causes are known for eleven. HSP is caused by degeneration of the upper motor neurons in the brain and spinal cord. Clinically, HSPs can be divided into two main groups: pure and complex forms. Pure HSPs are characterized by slowly progressive lower extremity spasticity and weakness, often associated with hypertonic urinary disturbances, mild reduction of lower extremity vibration sense and, occasionally, of joint position sensation. Complex HSP forms are characterized by the presence of additional neurological or non-neurological features. The hallmark of HSP is progressive difficulty walking due to increasingly weak and stiff (spastic) muscles. Symptoms appear in most people between the second and fourth decade of life, but they can start at any age. Most people with HSP have uncomplicated HSP. There are also rare, complicated forms, which have additional symptoms, such as peripheral neuropathy, ichtyosis (a skin disorder) epilepsy, ataxia, optic neuropathy, retinopathy, dementia, mental retardation, deafness, or problems with speech, swallowing or breathing. There is no way to predict rate of progression or severity of symptoms. Generally, once symptoms begin, progression continues slowly throughout life. HSP rarely results in complete loss of lower limb mobility. HSP cannot be prevented, slowed or reversed, but treatments can relieve some of the symptoms and help the person manage day-to-day activities. Symptomatic management of the disease includes myorelaxing medication and functional rehabilitation.

PARTICIPANTS IN THE SURVEY

The countries most represented amongst respondents concerned with SCD include Germany (23), Denmark (16) and France (6).

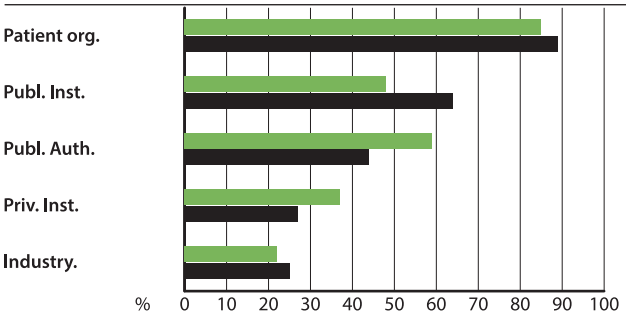
A total of 54 survey participants reported being concerned with HSP. The results below highlight major differences in opinion from HSP respondents compared to other disease groups. As such, only a few results specific to HSP are presented. For the remainder of survey questions, HSP respondents did not differ significantly in their responses.

AIMS OF A REGISTRY



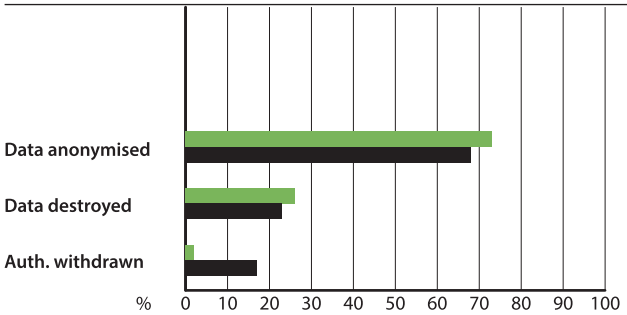
HSP respondents more frequently reported a preference for the description of the disease (40.1%) and support for CT recruitment (33.3%) and less frequently reported a preference for treatment evaluation (22.2%) as important registry aims.

REGISTRY USERS/ACCESS



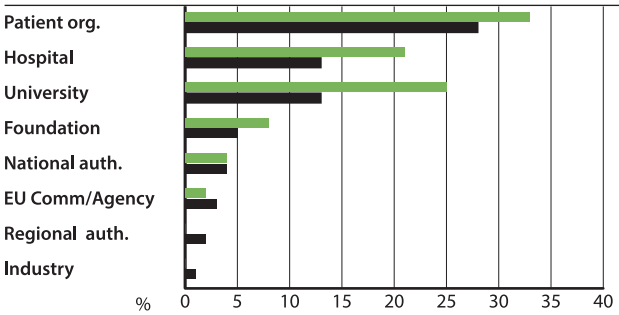
HSP respondents more frequently expressed a preference for public authorities (59.3%) and private citizens or institutions (37.0%) to have access to registry data as compared to most respondents.

WITHDRAWAL FROM A REGISTRY



HSP respondents reported a preference for anonymising their data for future research following the withdrawal from a registry even more frequently (72.6%) than other respondents.

INITIATIVE FOR ESTABLISHING A REGISTRY



HSP respondents that knew of the existence of a registry for their disease, more frequently reported universities (25.0%) and hospitals (20.8%) as the initiator as compared to other respondents.

NEUROFIBROMATOSIS

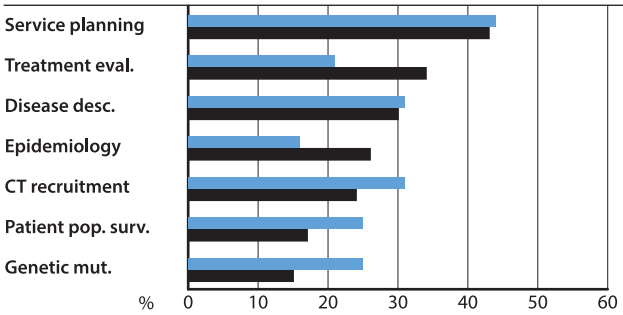
CLINICAL PICTURE

Neurofibromatosis (NF) is a genetic neurological disorder that can affect the brain, spinal cord, nerves and skin. Tumours, or neurofibromas, grow along the body's nerves or on or underneath the skin. There are three types of neurofibromatosis. Neurofibromatosis type 1 (NF1) causes skin changes and deformed bones and usually starts at birth. Neurofibromatosis type 2 (NF2) causes hearing loss, ringing in the ears and poor balance. It often starts in the teen years. Schwannomatosis is the third and rarest type and less well understood in terms of natural history and inheritance (mostly sporadic). Schwannomatosis causes intense pain. Usually the tumours are benign, but sometimes they can become cancerous. It is the rarest type and it is.
There is no cure for NF and treatment is aimed at controlling symptoms. Depending on the type of disease and how bad it is, treatment may include surgery to remove tumours, radiation therapy and medicines. Type 1, in particular, is so varied in its manifestation, that it is difficult to predict outcome, as phenotype is so variable even within affected families. Most people with NF1 lead relatively long and healthy lives, but it does reduce life expectancy by around 15 years.
he major complications are hypertension and malignancy. NF2 generally has a worse prognosis. Much of the morbidity from these tumours results from their treatment.
Early detection and prompt attention to complications may reduce overall morbidity and mortality.

Age of onset	
Prevalence	+
Genetic Nature (inheritance)	
Number of Regional, National, European or International Registries	25

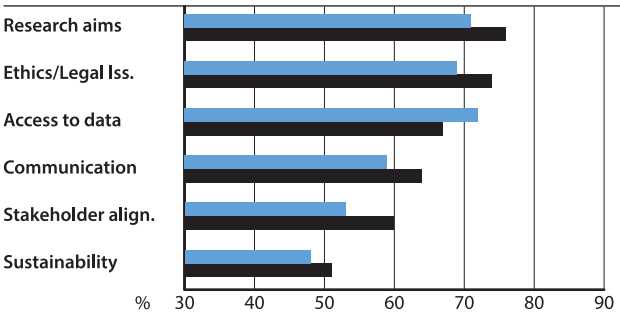
PARTICIPANTS IN THE SURVEY

The countries most represented amongst respondents concerned with NF include Denmark (19), Greece (12) and Italy (6).
A total of 54 survey participants reported being concerned with NF. The results below highlight major differences in opinion from NF respondents compared to other disease groups. As such, only a few results specific to NF are presented. For the remainder of survey questions, NF respondents did not differ significantly in their responses.



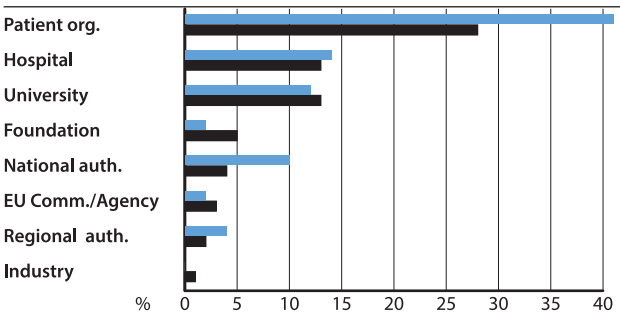
AIMS OF A REGISTRY

NF respondents less frequently reported a preference for treatment evaluation (20.8%) and more frequently for genetic mutations (24.5%)



REGISTRY GOVERNANCE

Overall, NF respondents less frequently reported the importance of a patient perspective in the governance of a registry as compared to other respondents except for the aspect of access to data (71.9%)



INITIATIVE FOR ESTABLISHING A REGISTRY

NF respondents that knew of the existence of a registry for their disease, more frequently reported patient organisations (40.8%) and national authorities (10.2%) as initiators of a registry as compared to other respondents.

SCLERODERMA

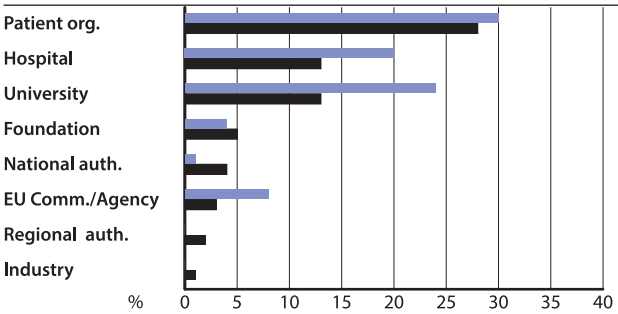
CLINICAL PICTURE

Scleroderma (SCD) is a group of rare autoimmune, widespread connective tissue diseases that involve changes in the skin, blood vessels, muscles, and internal organs.
There are two main types. Localized scleroderma affects only the skin and is characterized by fibrosis of the skin causing cutaneous plaques or strips. Systemic SCD is a generalized disorder affecting the blood vessels and internal organs (particularly, lungs, heart, and digestive tract), as well as the skin. Women are predominantly affected. Although the cause of SCD is unknown, it is believed to be related to an overproduction and accumulation of collagen which results when the immune system turns against the body (autoimmune reaction). SCD can take several different forms, and even within the same form the progression and severity of symptoms can vary greatly from patient to patient. In some patients, symptoms will develop with a surprising rapidity while, in others, symptoms may take years to develop and can even experience periods when the disease is almost in remission. At present, there is no known cure for SCD, but there are means and treatments available to help patients manage the symptoms. Due to the varied nature of the disease, the response to each treatment is from person to person.

Age of onset	
Prevalence	
Genetic Nature (inheritance)	
Number of Regional, National, European or International Registries	4

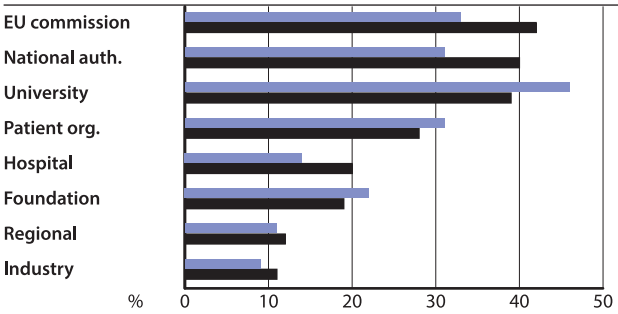
PARTICIPANTS IN THE SURVEY

The countries most represented amongst respondents concerned with SCD include Spain (38), Germany (15) and Italy (5).
A total of 77 survey participants reported being concerned with SCD. The results below highlight major differences in opinion from SCD respondents compared to other disease groups. As such, only a few results specific to SCD are presented. For the remainder of survey questions, SCD respondents did not differ significantly in their responses.



INITIATIVE FOR ESTABLISHING A REGISTRY

SCD respondents that knew of the existence of a registry for their disease, most frequently reported patient organisations (29.6%) or universities (23.9%) as the initiator.



LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY

SCD respondents most frequently favoured universities and research institutes (46.2%) in assuring the long-term financial sustainability of a registry. Only 32.9% favoured the European Commission/EU Agency in assuring this sustainability.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

SCD respondents agreed more frequently than overall respondents (88.4%) with the proposal of a European legislation to uniformly regulate RDPR across Europe. Some respondents had no opinion (7.2%) and a few (4.3%) disagreed.

COMMON EUROPEAN REGISTRY INFRASTRUCTURE

SCD respondents agreed even more frequently than overall respondents (91.3%) with the establishment of a common portal European Commission and Member States for all RDPR in Europe.

SPINAL MUSCULAR ATROPHY

CLINICAL PICTURE

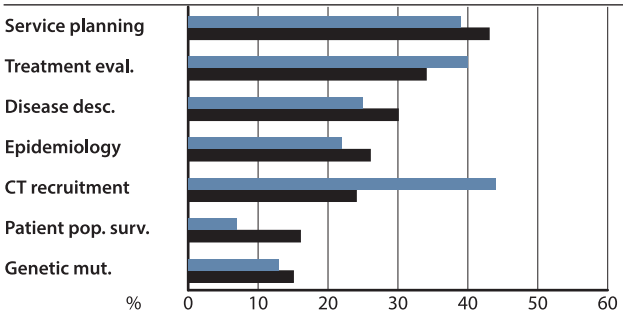
Spinal muscular atrophy (SMA) is a group of inherited disorders that cause progressive muscle degeneration and weakness. It is caused by a loss of specialized nerve cells, called motor neurons, in the spinal cord and the part of the brain that is connected to the spinal cord (the brainstem). Four subtypes have been defined according to the age of onset and severity of the disease: type 1 (SMA1), the most severe form, with onset before six months of age; type 2 (SMA2), with onset between 6 and 18 months of age, type 3 (SMA3), with onset between childhood and adolescence, and type 4 (SMA4), the least severe form, with adult onset. All types are characterized by muscle weakness and atrophy of varying severity, particularly affecting the lower limbs and respiratory muscles. The loss of motor neurons leads to weakness and wasting (atrophy) of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases, the muscles used for breathing and swallowing are affected. Death may occur due to respiratory insufficiency and infections. Clinical trials are ongoing to identify potential drug treatments for SMA, however, at present, management remains symptomatic, involving a multidisciplinary approach that aims to improve quality of life. The prognosis depends on the severity of the disease, which generally correlates with the age of onset: earlier-onset forms are generally associated with a poor prognosis, whereas life expectancy may be close to normal in later-onset forms.

Age of onset	
Prevalence	+
Genetic Nature (inheritance)	XX
Number of Regional, National, European or International Registries	24

PARTICIPANTS IN THE SURVEY

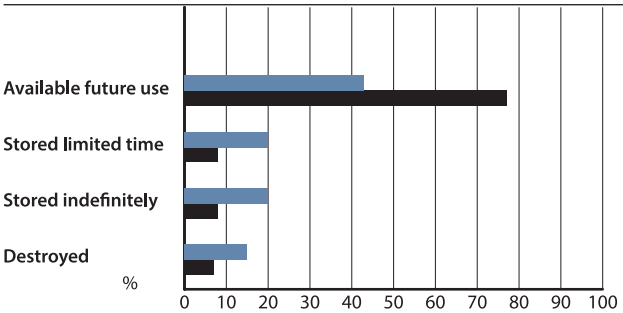
The countries most represented amongst respondents concerned with SMA include France (21), Czech Republic (13) and Spain (8).
A total of 51 survey participants reported being concerned with SMA. The results below highlight major differences in opinion from SMA respondents compared to other disease groups. As such, only a few results specific to SMA are presented. For the remainder of survey questions, SMA respondents did not differ significantly in their responses.

AIMS OF A REGISTRY



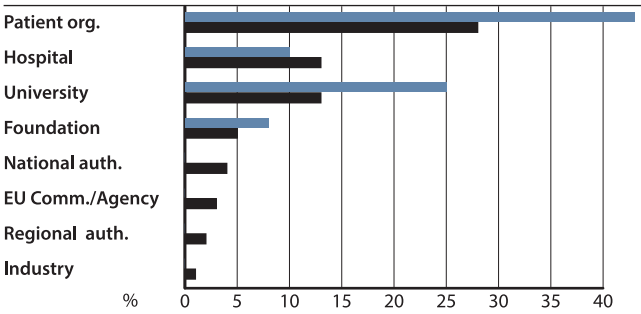
SMA respondents more frequently reported a preference for support for clinical trial recruitment (44.4%) and treatment evaluation (39.9%) and as important registry aims as compared to most other respondents.

REGISTRY CLOSURE



SMA responses reflected a less frequent preference (43.4%) to make data available to other registries or the research community and more frequently preferred data to be stored for an indefinite time (19.6%), stored for a limited time (19.6%) or destroyed (15.2%) upon a registry's closure as compared to most other respondents.

INITIATIVE FOR ESTABLISHING A REGISTRY



SMA respondents that knew of the existence of a registry for their disease, more frequently reported patient organisations (42.5%) and universities (25.0%) as the initiator of the registry as compared to most other respondents.

COMMON EUROPEAN REGISTRY INFRASTRUCTURE

SMA respondents less frequently agreed (74.3%) with the establishment of a common European Commission and Member States portal for all RDPR in Europe.

TUBEROUS SCLEROSIS

CLINICAL PICTURE

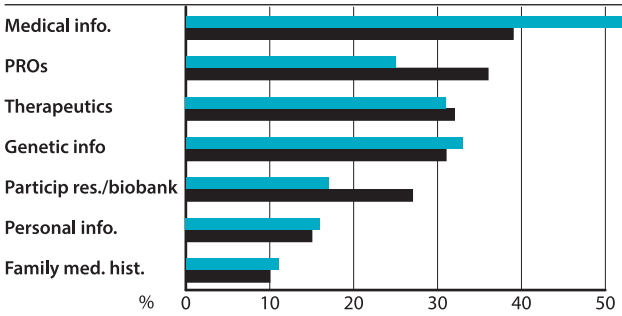
Tuberous sclerosis (TS) is a genetic disorder characterized by the growth of numerous noncancerous (benign) tumours in many parts of the body (brain, eyes, heart, kidneys or lungs). These tumours can cause neurological symptoms such as epilepsy, mental retardation and behavioural problems, as well as kidney disease, lung disease, skin abnormalities and vision problems. Some tumours can cause serious complications (e.g., those affecting the brain, heart, or kidney). TS results from mutations in one of two genes (TSC1 and TSC2), which play a role in cell division and in the production of proteins that suppress tumour growth. Individuals with mild forms of tuberous sclerosis do not have a shortened life expectancy while individuals with more severe forms may have serious disabilities. Complications in some organs such as the kidneys and brain can lead to severe difficulties and even death if left untreated. To reduce these dangers, people with TS should be monitored throughout their life by their physician for potential complications. There is no cure for TS, but thanks to research findings and improved medical therapies, people with tuberous sclerosis can expect improved health care. Early intervention is helping to overcome developmental delays. Advancements in research are bringing new and improved therapeutic options such as surgery to remove tumours or stop tumour and new therapies to help control seizures.

Age of onset	
Prevalence	+
Genetic Nature (inheritance)	
Number of Regional, National, European or International Registries	19

PARTICIPANTS IN THE SURVEY

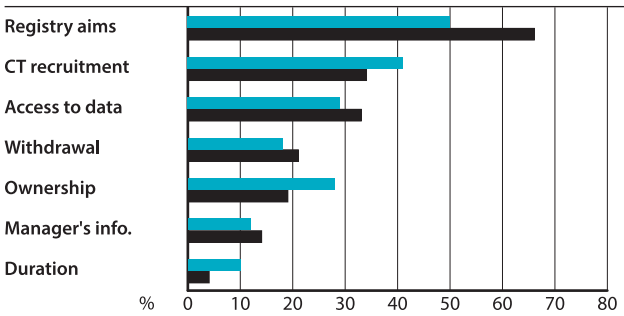
The countries most represented amongst respondents concerned with TS include Greece (18), Spain (17) and Italy (8).

A total of 50 survey participants reported being concerned with TS. The results below highlight major differences in opinion from TS respondents compared to other disease groups. As such, only a few results specific to TS are presented. For the remainder of survey questions, TS respondents did not differ significantly in their responses.



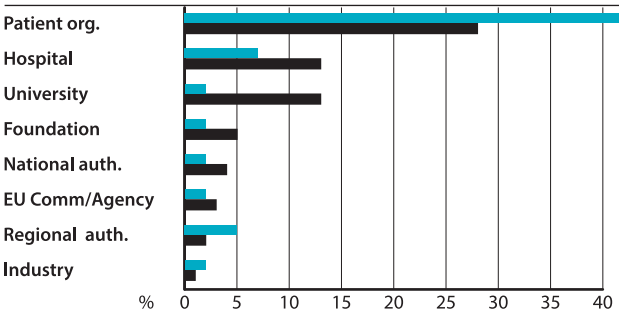
TYPES OF INFORMATION COLLECTED IN A REGISTRY

TS respondents more frequently communicated the importance of collecting medical information (60.4%) and less frequently communicated the importance of collecting information on patient reported outcomes (25%) or patient participation in clinical research or a biobank (17.4%) than most other respondents.



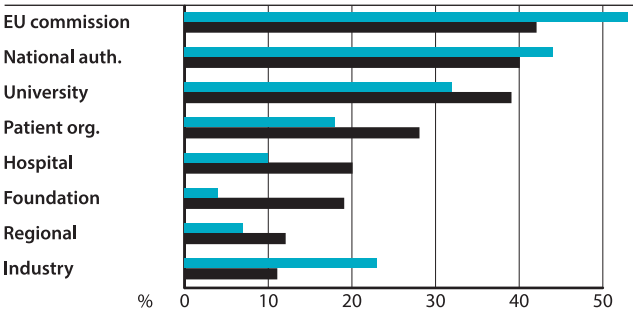
INFORMATION COMMUNICATED UPON ENROLMENT IN A REGISTRY

TS respondents differed in the overall ranking of the types of information communicated to patients participating in registries. The preference for information about registry aims was less frequently reported (50.0%) and information on custodianship of the registry (27.5%) more frequently reported amongst TS respondents as compared to other respondents.



INITIATIVE FOR ESTABLISHING A REGISTRY

TS respondents that knew of the existence of a registry for their disease, most frequently reported patient organisations (55.8%) as the initiator.



LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY

TS respondents more frequently favoured the European Commission/EU Agency (53.3%) and industry (23.0%) in assuring the long-term financial sustainability of a registry as compared to other respondents.

WILLIAMS SYNDROME

CLINICAL PICTURE

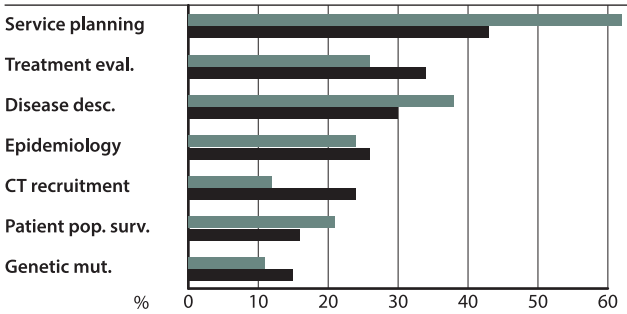
Williams syndrome (WS) is a rare genetic disease characterised by narrowed arteries leading to cardiovascular problems, mental retardation, learning difficulties, a distinctive cheerful facial appearance, and unique behavioural and cognitive traits including being hyper-social, occasional negative outbursts, sensitivity to noise, gifted in music, lack of depth perception and an inability to visualize how different parts assemble into larger objects. Characteristic physical features of WS include puffiness around the eyes, a short nose, wide mouth, full cheeks and lips, a small chin, a long neck, sloping shoulders, short stature, limited mobility in their joints, and curvature of the spine. The onset of symptoms usually begins with physical characteristics, irritability, colic, and feeding problems and progresses to abdominal pain in adolescents, and diabetes, high blood pressure, heart failure and hearing loss in adults. Medical complications associated with the disorder may shorten the lifespan of some people with WS. Treatment is based on the individual's symptoms, but usually includes monitoring of cardiovascular problems. Despite the many challenges of living with WS, daily life for patients and their families can be very enjoyable. People living with WS are extremely outgoing, kind and caring and are very tuned in to other people's feelings, wanting everyone to be happy.

Age of onset	
Prevalence	
Genetic Nature (inheritance)	
Number of Regional, National, European or International Registries	11

PARTICIPANTS IN THE SURVEY

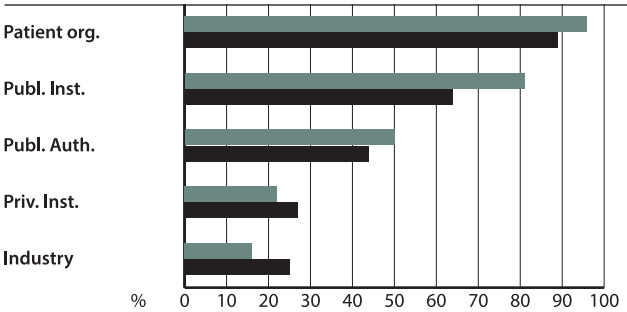
The countries most represented amongst respondents concerned with WS include France (32), Italy (30), Spain (19), Germany (19) and Hungary (10).
A total of 117 survey participants reported being concerned with WS. This represents the largest group of respondents per disease. The results below highlight major differences in opinion from WS respondents compared to other diseases. As such, only a few results specific to WS are presented. For the remainder of survey questions, WS respondents did not differ significantly in their responses.

AIMS OF A REGISTRY



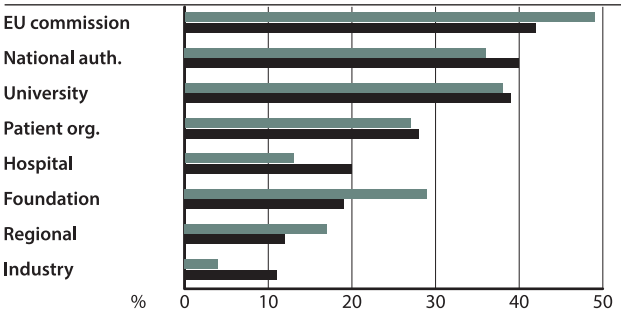
Respondents concerned with WS communicated a particularly strong preference for service planning (62.1%) and description of the disease (37.9%) as an important aim of a RDPR.

REGISTRY USERS/ACCESS



More than any other respondents, WS respondents almost unanimously agreed (95.7%) that patient organisations should have access to information contained in the register. They also responded more frequently that public institutions (81.0%) should have access to information than respondents of other disease groups.

LONG-TERM FINANCIAL SUSTAINABILITY OF A REGISTRY



Like other disease groups, respondents concerned with WS most preferred the European Commission/EU Agency (48.9%) as a source of funding for the long-term sustainability of RDPR. WS respondents favoured foundations (16.8%) and regional authorities (29.1%) as funding sources more than other disease groups. These respondents indicated even less frequently their preference for industry (3.9%) as a source of long-term sustainability.

UNIFORM EUROPEAN REGULATORY FRAMEWORK

WS respondents agreed more frequently than overall respondents (87.5%) with the proposal of a European legislation to uniformly regulate RDPR across Europe. Some respondents had no opinion (8.7%) and a few (3.8%) disagreed.

EXPLORATORY ANALYSIS

Using the Multiple Correspondance Analysis (MCA) technique, an exploratory analysis was performed to investigate the structure of any underlying relationships among characteristics of respondents (country of origin, characteristics of the disease they are affected with) and their opinions about elements of registries (i.e. responses to survey questions) especially where variability was observed in the descriptive analysis.

An initial MCA concluded in the elimination of the variable "country of origin" in the analysis because no clear relationship between a respondent's country of origin and typology of responses were found. Subsequently, country of origin was treated as a supplementary variable. The result suggested that country groups were strongly defined by disease characteristics of patients most likely due to the fact that patient organisations were directly involved in communicating the survey's existence to their constituents.
Patient organisations that were more effective in disseminating the survey, more strongly influenced the responses from the perspective of a person living with the disease they represented.

Figure 1 represents the plot defined by the characteristics of the disease respondents were affected with.

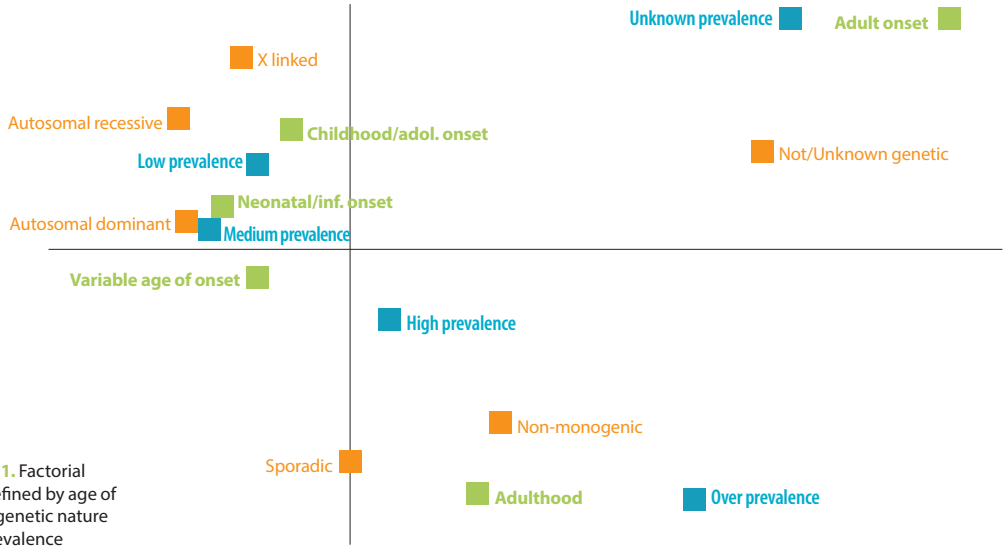


Figure 1. Factorial plan defined by age of onset, genetic nature and prevalence

This factorial plan can be interpreted as follows:

- The horizontal axis is defined by level of knowledge about the disease with higher level of knowledge on the left and lower level of knowledge on the right.
- The vertical axis is defined by age of onset (adult above and infancy/child below), genetic nature of the disease (known single gene genetic inheritance above) and caused by other modes of genetic inheritance or no or unknown genetic nature below) and prevalence (low/medium prevalence above and high prevalence below).
- As such, three groups of respondents emerge:

Top left quadrant: Respondents affected by diseases with earlier age of onset, lower prevalence and monogenic inheritance (X-linked, autosomal dominant, autosomal recessive)

Bottom right quadrant: Respondents affected by diseases with later age of onset, higher prevalence and diseases that are genetic but not inherited or multigenic)

Top right quadrant: Respondents affected by diseases with little knowledge (unknown prevalence, unknown age of onset and diseases with unknown causes or no genetic cause)

The total responses to the following questions were projected onto the factorial plan to observe tendencies:

- Aims of a Registry
- Types of Information Collected in a Registry
- Information Communicated Upon Enrolment in a Registry
- Withdrawal from a Registry
- Registry Closure
- Registry Users/Access
- Registry Governance
- Long-term Financial Sustainability of a Registry

REGISTRY AIMS

An association between preference for genetic and clinical research registry aims (as the most important possible aim) and respondents affected by monogenic diseases, lower prevalence and early onset was observed. Not surprisingly, an association for preference for epidemiological research and surveillance of the patient populations and respondents affect by later onset, higher prevalence and non-inherited or multigenic diseases was also observed (Figure 2).

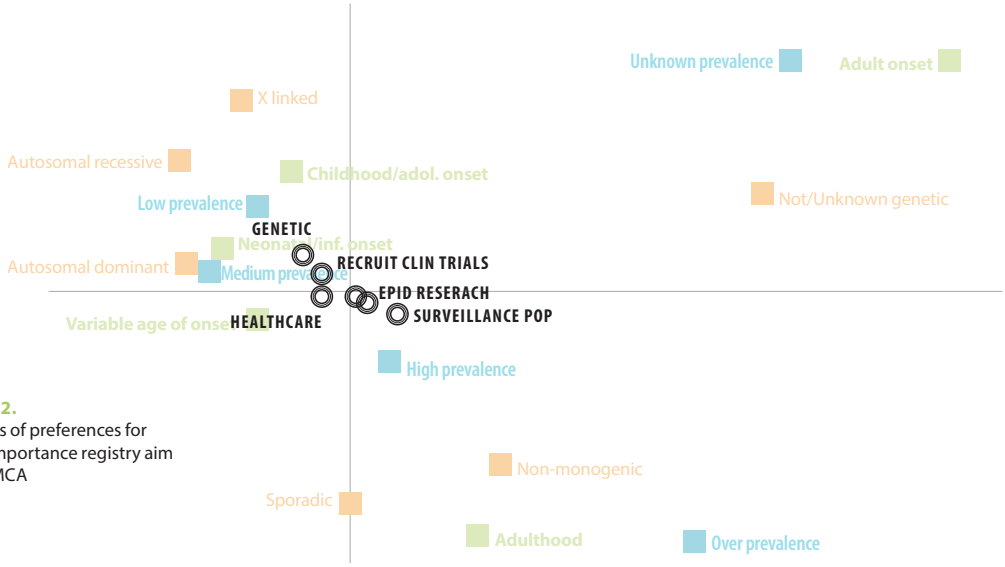


Figure 2.
Analysis of preferences for most importance registry aim using MCA

TYPES OF INFORMATION COLLECTED IN A REGISTRY

Similarly, respondents affected by disease with lower prevalence, earlier onset and monogenic in nature tended to prefer the collection of genetic and personal information. Longer-term outcomes requiring surveillance over time were associated more with respondents with later onset, non-monogenic and higher prevalence diseases (Figure 3).

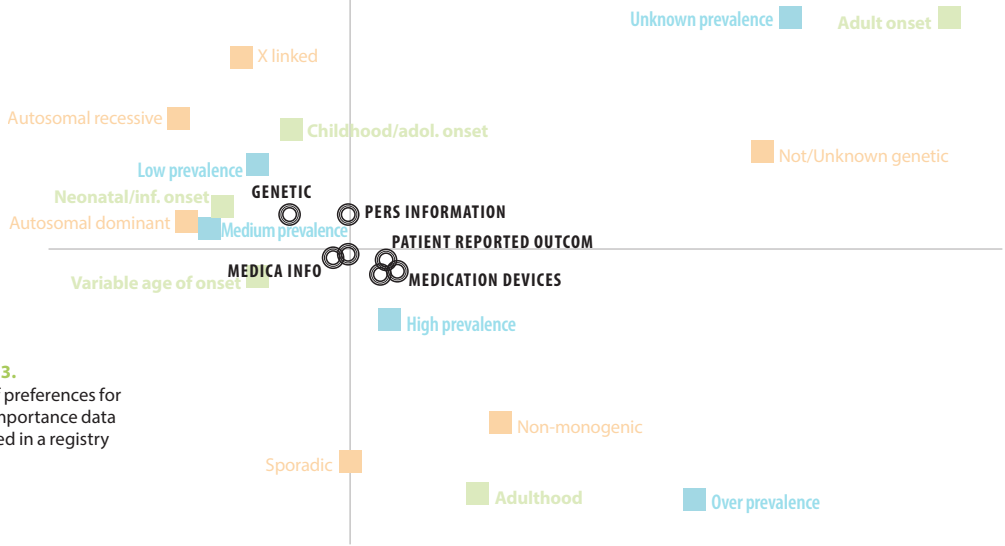


Figure 3.
MCA of preferences for most importance data collected in a registry

REGISTRY USERS/ACCESS

Less variability was observed between preferences for type of user access to data and disease characteristics, although respondents affected by disease with early onset, lower prevalence and monogenic nature tended to prefer access to data for industry more than other respondents (Figure 4).

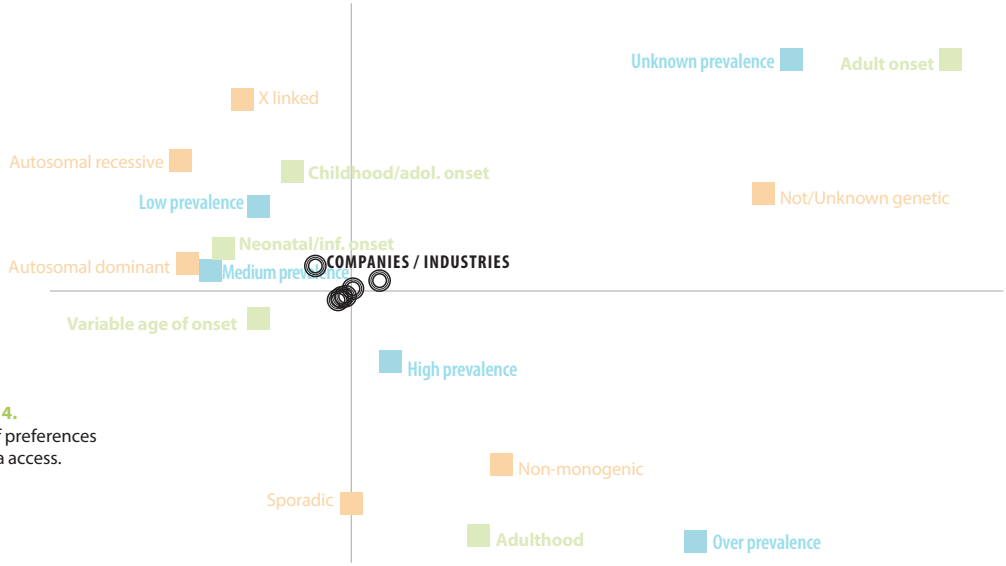


Figure 4.
MCA of preferences for data access.

INFORMATION COMMUNICATED UPON ENROLMENT IN A REGISTRY

Less variability was observed regarding associations between preferences for information communicated to a patient upon enrolment in the registry and characteristics of the disease with which the respondent was affected. Respondents affected by diseases with little knowledge about them (unknown prevalence, unknown prevalence, no or unknown genetic inheritance) did show a slight tendency to prefer having information on data ownership more frequently (Figure 5).

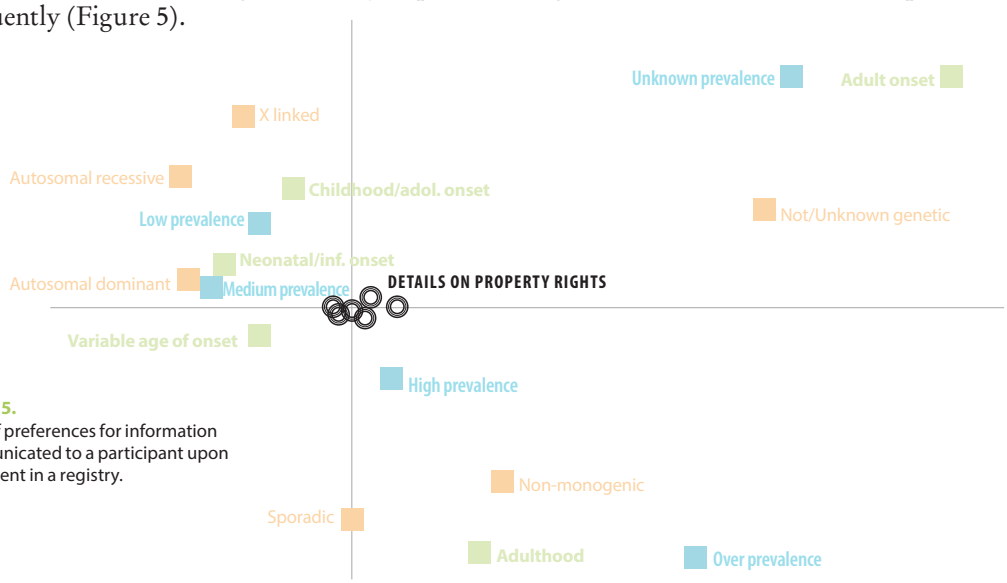


Figure 5.
MCA of preferences for information communicated to a participant upon enrolment in a registry.

REGISTRY GOVERNANCE

No variability was observed in the association between preferences and characteristics of the disease with which the respondents were affected (Figure 6).

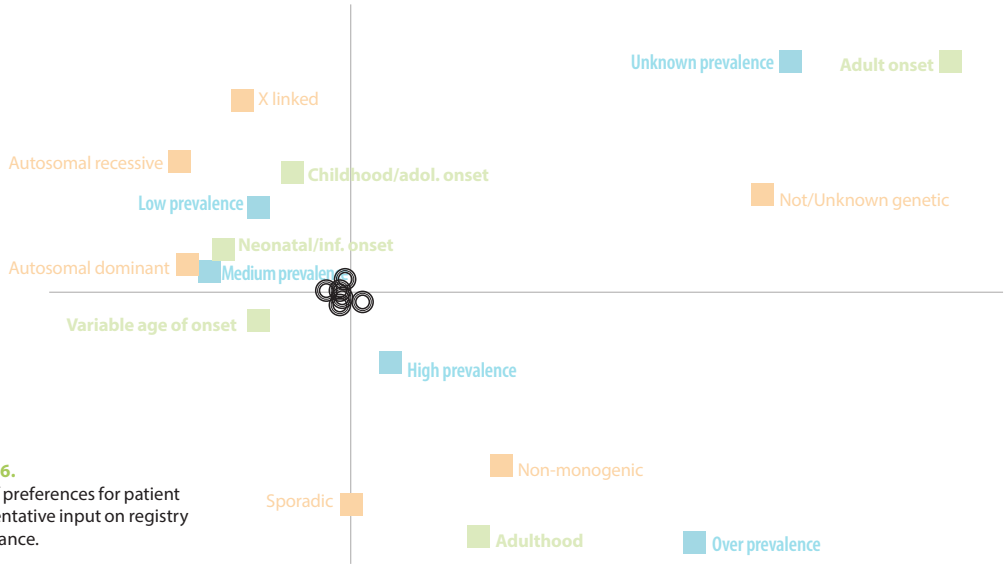


Figure 6.
MCA of preferences for patient representative input on registry governance.

LONG-TERM FINANCIAL SUSTAINABILITY

Low variability was observed. No strong association between preference for the ensuring of the long-term financial sustainability of a registry and disease characteristics of respondents (Figure 7).

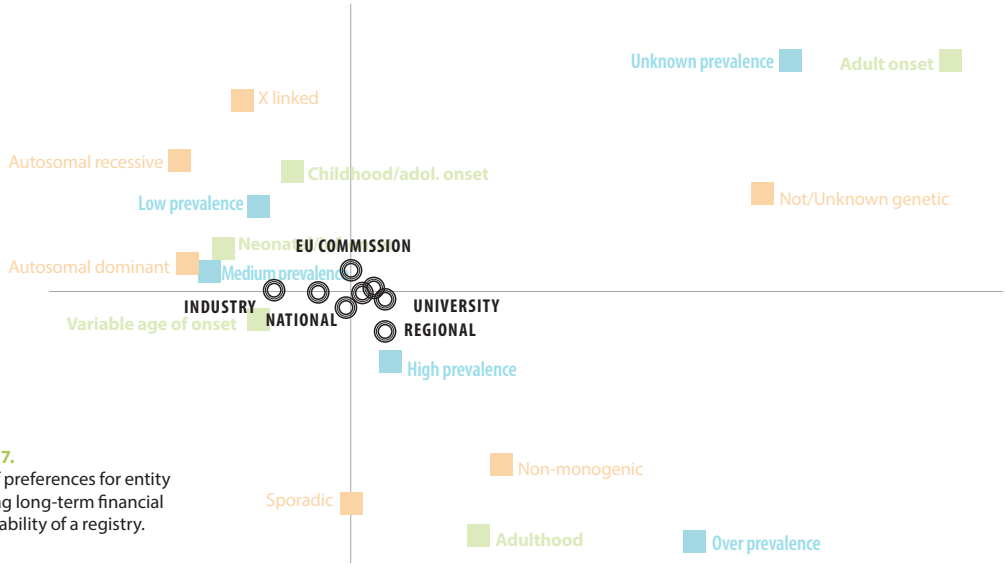


Figure 7.
MCA of preferences for entity ensuring long-term financial sustainability of a registry.

CONCLUSIONS

The MCA confirmed that for questions in which little variability was observed in the descriptive analysis, it can ultimately be concluded that consensus exists amongst most respondents, regardless of the disease they are affected by. For other elements of rare disease patient registries, variability amongst respondent preferences does indeed exist across characteristics of diseases. Nevertheless a trend is consistently observed aligning a group of preferences with respondents affected by diseases with earlier age of onset, lower prevalence and monogenic inheritance and yet other preferences with respondents affected by diseases with later age of onset, higher prevalence and diseases that are genetic but not inherited or multigenic.

The policy impact of these findings suggests that national preferences and disease-specific preferences can sometimes be addressed by a common European registry infrastructure. For other preferences, national, regional and disease specific initiatives may be more appropriate.

«The time for regional registries has come and gone. Global is the future.»

«There is an urgent need for a central resource that is well regulated, funded and which meets all legal and ethical requirements to ensure patient confidence.»

CONCLUSIONS

«I understand that it may be important to have an inventory of rare diseases and patients to get a better understanding of the disease and to improve their conditions of life, their health and their social, economic and institutional support. «

The respondents of this survey have a clear vision on the importance of registries in collecting crucial data in advancing quality care, research and therapeutic development for the diseases with which they are living. The results of the EPIRARE Patient Survey directly reflect a collective, growing enthusiasm from patients and their representatives to directly participate in rare disease patient registries but also to be involved in and directly contribute to their development, maintenance, governance and sustainability at the national and European levels.

However, some variability emerged across countries, disease groups and disease characteristics that represent distinct needs. For example, for preferences regarding the structure of a registry (registry aims and the type of information collected) variation was observed across country and disease groups particularly for elements other than those most frequently and least frequently preferred overall. This variation was investigated in the exploratory analysis preceding these conclusions and suggests a spectrum of preferences from more clinical/translational research aims and data collection towards public health aims and data collection.

A potential relationship can be evoked between disease characteristics and these preferences where respondents concerned with a disease monogenetic in nature, with low prevalence and early onset, more often reported a preference in clinical/translational research aims and data collection while survey participants affected by diseases with higher prevalence, later onset and a non-monogenetic nature or non-inherited basis showed a preference towards more public health aims and data collections. It is not surprising that patients and their representatives

more frequently prioritise clinical/translations registry aims and data types if affected by diseases with an identified cause and thus likely potential for therapy. It also not surprising that for diseases affecting young children the race to discover effective treatments is that much more critical. Similarly, it can be concluded that patients or representatives of patients with adult onset diseases or with less knowledge about the cause and thus potential curative treatments, may see quality of life and healthcare delivery aims as more of a priority.
Variability with respect to industry access to data followed the same trend, where the exploratory analysis points to a relationship between lower prevalence, earlier onset and monogenetic diseases and preference for data access for industry. Again, priorities in clinical/translational research could explain the association. Subsequently, it could be concluded that registries with clinical/translational research aims may need to remain focused on groups of rare diseases with similar characteristics.

But for many issues, there is a clear consensus illustrated by a high overall number of responses and little variability over country or disease groups. Respondents consistently reported their highest preference for a registry's aims as healthcare and social planning. It follows that respondents also consistently ranked medical information as the most important type of information to collect in a registry.

This strong consensus around the structure and uses of patient data brings forward the need for a careful balance in patient rights and societal "duties" in research participation. The EU Charter of Fundamental Rights outlines patient rights to privacy of sensitive data, the right to participate freely in research and to contribute data in the name of solidarity. But it also recognizes the right of access to preventive health care and benefit from medical treatment. The very valuable and scientifically useful patient data collected in registries belongs to people living with rare diseases – individual people who overcome great obstacles to access healthcare and social services. It is thus critical that any activity in patient registration and data collection respects the needs and expectations of individual participants by guaranteeing that the benefits of research are directed towards them.

As concerns the access to registry data for patient organisations, respondents varied little in their highest preference for the aim of healthcare and social planning. Even more consensual were the responses to questions regarding future use of data upon a registries closure or an individual patient's withdrawal from a registry. In both cases the majority of respondents reported, with little variability, a preference to make the most of their data by making it availability to other registries or the research community upon a registries closure or requesting an anonymisation of data for potential, future research upon withdrawal. In order to be truly and adequately informed to participate in a registry, respondents consistently reported a desire to understand the aims of the registry in which they will enrol. Understandably, respondents also reported the highest preference for being involved in determining a registry's aims as a member of its governance board.

The patient should remain the owner of his or her data without needing authorisation by a medical professional or other to access it. It is essential that a patient have access to this information and be informed of finding produced as a result of it…

This finding has significant implications in driving better adapted national and European policies on rare disease patient registries. Difficulty in accessing health and social care has been well documented amongst rare disease patients in Europe[1] frequently explained by healthcare systems that are poorly adapted for the specific needs of rare diseases.

I would like, as a patient and as a computer technician, a register with two levels of indexing. One would be very public and transparent, containing epidemiological data and characteristics of the disease in individual patients. The other would be absolutely private, accessible only to authorized personnel and to the patient himself, and would connect the above data to an individual person, who will determine, from his own will, to whom and to what purpose he wants to give access to these data.

The respondents of this survey and the rare disease patient community at large clearly recognise the utility of rare disease patient registries in collecting such information and analysing it to better adapt current healthcare and social services. A major outcome of the EPIRARE project[2] is the description of the current landscape in rare disease patient registration and the specific finding that the majority of registries do not have the aim of healthcare and social planning. One solution to bridging this gap is the increased inclusion of patient representatives in the governance structures of national and European level rare disease patient registries. Patients and patient representatives have demonstrated their consistent capacity as equal stakeholders in rare disease patient registries and many examples exist of the benefits of the inclusion of patient representation.[3]

Regarding expectations for guaranteeing long-term financially stability of a registry, respondents reported trust in public entities such as the European Commission or another EU agencies, national health authorities and universities or research institutes in this role. Most unvaryingly, the significant majority of respondents reported favouring the proposal for a uniform regulatory framework for registries across European and a common European Registry portal. The patient community expects these central resources to improve healthcare and social planning, to increase accessibility to high quality data, to include the patient community in its governance, to well inform patients of its aims and the objectives of research projects based on the data, to be publically funded and meet all legal and ethical requirements to ensure patient confidence. These frequently shared expectations can define the characteristics of a common European initiative and a common regulatory framework in rare disease registration and data collection. Even for elements without complete consensus, a centralised initiative would remain adequately flexible to link to certain activities that remain more geographically local or disease-specific or be adequately adaptive to incorporate new data elements and corresponding procedure as consensus was reached over time.

Whether at European or national levels, the patient community clearly wishes to be involved in many aspects of the patient registration process. In order to increase the patient community's trust towards patient registries and increase their long-term financial support, patient organisations expect transparency in the use of registry data and results of research results.
In many cases, patient organisations can directly benefit from access to registry data to support advocacy activities. Patients and their representatives can concretely contribute to the aims and individual elements included in a registry and to influence all elements of governance such as data access policies. Patient organisations can also prepare general information for patients and the general public, assemble informed consent materials and recruit patients and health professionals to participate. Above all, the quality of data collection and patient registration can only be improved with increased patient participation and best practices that most effectively bring direct benefit for patients.

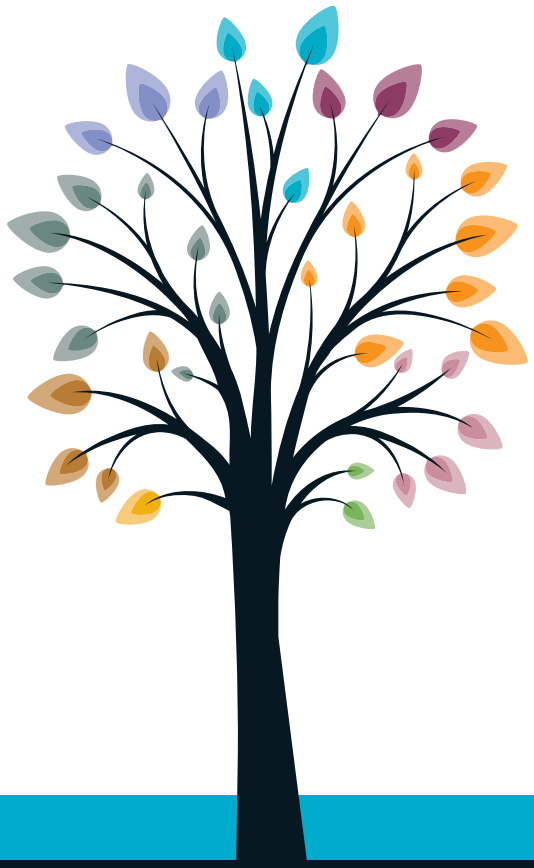
1 - Kole A, Faurisson F., Rare diseases social epidemiology: analysis of inequalities. Adv Exp Med Biol. 2010;686:223-50 //
2 - The EPIRARE Survey, http://www.epirare.eu // 3 - TREAT-NMD Neuromuscular Network, http://www.treat-nmd.eu/

THE WAY FORWARD

For the last decade, EURORDIS' advocacy actions in the area of rare disease patient registries have been driven by an interactive consultation process. Alongside its mission to be the voice of patient organisations and people living with rare diseases at the European level on this subject, EURORDIS has continued to build their capacity with the ultimate goal of empowering the rare disease patient community to make informed decisions about rare disease patient registration and data collection. The results of this survey represent a capstone to an intensive work-in-progress to consult the patient community on their expectations and experiences as well as the creation of a cohesive, patient-centric, advocacy tool instrumental in promoting sound policies in rare disease patient registries in Europe.

Clearly people living with rare diseases are motivated in advancing care, research and drug development for the diseases with which they live. The scarcity of relevant knowledge and experience with most rare diseases creates a particularly critical need for cooperation and infrastructure building in patient registration and data collection. Patients recognise the importance of registries as key determinants in accelerating these advancements. EURORDIS actively advocates on their behalf by underscoring the importance of data-sharing and collaboration across stakeholders and across Europe in achieving strong economies of scale, broader scope and long-term knowledge generation.

In reality, distinct objectives and needs for rare disease patient registries exist and will continue to exist across each stakeholder, each disease area and each country or region. Today, EURORDIS is participating in several promising multi-stakeholder and multinational initiatives supported by the European Commission to propose a range of solutions to improve use of the limited available resources and to accelerate progress in patient registration and data collection.



EURORDIS INVOLVEMENT IN RARE DISEASE PATIENT REGISTRY INITIATIVES

Supporting National Initiatives for Rare Disease Patient Registries

The European Union has recommended that "Member States should consider supporting at all appropriate levels, including the Community level, on the one hand, specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance"

As a major partner in the European Project for Rare Diseases National Plans Development (EUROPLAN), EURORDIS and rare disease National Alliances have, thus far, organised 35 conferences on national plans for RARE DISEASES in 21 EU Member States together with national competent authorities and all stakeholders on six main policy areas. One such area is healthcare and research, which includes recommendations that outline the importance for Member States to stimulate and support national initiatives in the domain of registries and the importance of their use for research, epidemiology and clinical purposes, and for health and social services planning. The recommendations go on to encourage these activities in a European or international framework in which registries established and managed by rare disease Centres of Expertise share data across European Reference Networks when they exist.

Adding Value to all Patient Registries across Europe

The Cross Border PAtient REgistries iNiTiative (PARENT Joint Action, 2012-2015) brings added value to patient registries by providing Member States with recommendations and tools for implementation of interoperable and cross-border enabled patient registries. One major aim of the PARENT Joint Action is to support Member States in developing comparable and coherent patient registries in fields where this need has been identified (e.g. chronic diseases, rare diseases, medical technology). Another is to support Member States in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy and effectiveness of health technologies. EURORDIS is a member of the Associated Project Group, which participates in the project's Plenary Assembly to review and comment on strategic decisions made by the project Executive Committee. Specifically, EURORDIS will support the integration of needs specific to rare diseases within the future context of a broad European Infrastructure on Registries for all diseases.

Keeping abreast of emerging good practices on patient registries at large, EURORDIS will also contribute to the policy scenario and technical guidance ensuring specific needs particular to rare disease patient registries are foreseen.

Integrating Databases, Registries, Biobanks and Clinical Data through RD-Connect

The RD-Connect project (2012-2016) will provide an integrated, user-friendly platform, built on efficient informatics concepts already implemented in international research infrastructures for large-scale data management. It will also safely and ethically provide access to federated databases/patient registries, biobank catalogues, harmonised -omics profiles and cutting-edge bioinformatics tools for data analysis. One important achievement of the project will be the implementation of state-of-the-art data sharing practices such as the use of a global unique identifier (RD-ID) to de-identify patient data while keeping the link to the corresponding biospecimen and –omics data sets.

EURORDIS is a full partner in the RD-Connect project and will directly contribute to these activities from the patient perspective, to support the involvement of patient organisations, to build their capacity on registries, biobanking and -omics, to ensure a strong interaction and coordination of the RD-Connect network with other initiatives within and beyond Europe, and to disseminate project outcomes internationally.

Fostering International Collaboration in the Field of Rare Disease Research - IRDiRC

The International Rare Disease Research Consortium (IRDiRC) was initiated by the European Commission and the US National Institutes for Health Research in April 2011 to foster international collaboration in order to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases by the year 2020. IRDiRC objectives in the field of rare disease patient registries include encouraging transatlantic integration and increased collaboration through the feasibility of meta-registries or a registry of registries.
As a member of the Executive Committee, of the Therapeutic Scientific Committee, and of the Registries and Natural Histories Working Group, EURORDIS is actively involved in bringing forward the needs and concerns of people living with rare diseases on the subject of rare disease patient registries amongst others to ultimately drive forward IRDirC goals of improved health through better diagnoses and therapies.

Encouraging Patient-Centric Data Collection Initiatives

As enthusiasm around the power of data collection and patient registration grows, other innovative models of data sharing are also surfacing. Of particularly important note is the emergence of patient-driven initiatives in Europe. Initiation of a registry by patient organisations is a key element without which registries for many rare diseases would not exist. Many patient groups across Europe are already very active and many more are capable of acting in this role.

Still more registries, whether initiated by patient organisations or not, include patient-entered data. A number of trends including increased survival rates, recognition that treatment should increase life expectancy as well as improve quality of life, limited correlation between morbidity and patient satisfaction and demand for more engagement of patients in decision-making and self-care help explain the emergence of patient-reported information as an important measure in rare disease health services and treatment development.
Specific concepts directly reported by patients in registries often include:

- Demographic information
- Overall health status
- Symptoms/signs, individually or as a syndrome, associated with a medical condition
- Functional status or health-related quality of life (physical, psychological or social)
- Health perceptions
- Satisfaction with treatment or preference for treatment
- Adherence to medical treatment
- Socio/economic impacts

The inclusion of this newly emerging data source will support the transformation of the role of the patient from that of subject to one of partner in research infrastructure building, where patient-reported data will be integrated to enhance conventional methods of observational research in rare diseases.

Contributing to European Platform for Rare Disease Registries

The European Commission has announced its strategic objective in creating a European Platform on Rare Diseases Registration (the Platform) providing common services and tools for the existing (and future) rare disease registries in the European Union. In the EPIRARE project, EURORDIS was responsible for consulting and building consensus in the patient community to address regulatory, ethical and technical issues associated with the establishment and management of rare disease patient registries in Europe. EURORDIS, being the leader of the EPIRARE Work Package responsible for drafting the policy scenarios on the aims, scope, governance structure and long-term sustainability of the Platform, significantly contributed to the proposal for the constitution of an EU registry Platform offering services for existing and new registries and linking EU wide important data on rare diseases.

• AIMS

The overall aim of establishing the Platform is to collect rare disease patient data within a common technical, regulatory and ethical reference framework at the EU level that will avoid wasteful fragmentation and duplication of time and resources, and facilitate the setting-up of more patient registries, especially for the rarest diseases. By addressing the scope, governance and long-term sustainability solutions at the EU level, synergies among different stakeholder interests can be maximised, ultimately best serving rare disease patients.

Specific aims of the Platform will include:

1. Overall promotion and support of best practices in the field of rare disease patient registration

2. Maximising access to rare disease patient data by establishing user-friendly and transparent services

3. Maximising utility of knowledge generated by meta- and individual registry analysis by establishing a service focused on connectivity and communication between affiliated registries

4. Providing common technical methods, tools, standards and support for existing registries and networks of data sources and – specifically a minimum common data set, quality standards, strategies and tools for monitoring and maintenance, ethical and legal guidelines

5. Providing technical methods, tools, standards and support to encourage the creation of new registries and data collection networks and improving existing ones - specifically a minimum common data set (fundamental for the implementation of a global unique identifier), quality standards, strategies and tools for monitoring and maintenance, ethical and legal guidelines

• SCOPE

By addressing the scope, governance and long-term sustainability solutions at the EU level, synergies among different stakeholder interests can be maximised, ultimately best serving all rare disease patients. The Platform should be rolled out in several phases reflecting the current heterogeneity in existing registries and short-term funding currently dedicated to guaranteeing its sustainability. A step-wise approach to the inclusion of affiliated registries will ultimately allow for coverage of all rare diseases (especially very rare) and patients (including those with no confirmed diagnosis).

All elements of the Platform including its scope (quality, access, use, governance, financial support) will evolve and adapt according to phases of development. The evolving scope of

the database will influence other aspects of the policies and procedures such as motivations for the affiliation of national, regional and disease specific registries. Overall, the Platform implementation should be to provide an added-value that:

- Builds a critical mass of data that will allow meta-analysis and comparison across diseases and countries
- Favours the emergence of new knowledge synthesized from data across groups of diseases
- Provides data collection solutions for extremely rare diseases for which no registries exist
- Provides data collection solutions for patients without a diagnosis
- Guarantees ethical and legal safeguards (from the legal and ethical point of view) and sustainability
- Exists as a non-profit public service base to lead in policies for data use and ownership that adhere to the highest standards

• GOVERNANCE

As the European Commission's in-house service providing it with science-based decision making, the Joint Research Centre (JRC) and specifically its Institute for Health and Consumer Protection (IHCP) will develop, house and execute all activities linked to the Platform in close collaboration with advisory boards and working groups comprised of pertinent stakeholders and experts in the field. The resulting governance structure will be adaptive to reflect anticipated and unforeseen changes in the landscape of rare disease patient registration including the Administrative Agreement between the European Commission and the JRC .

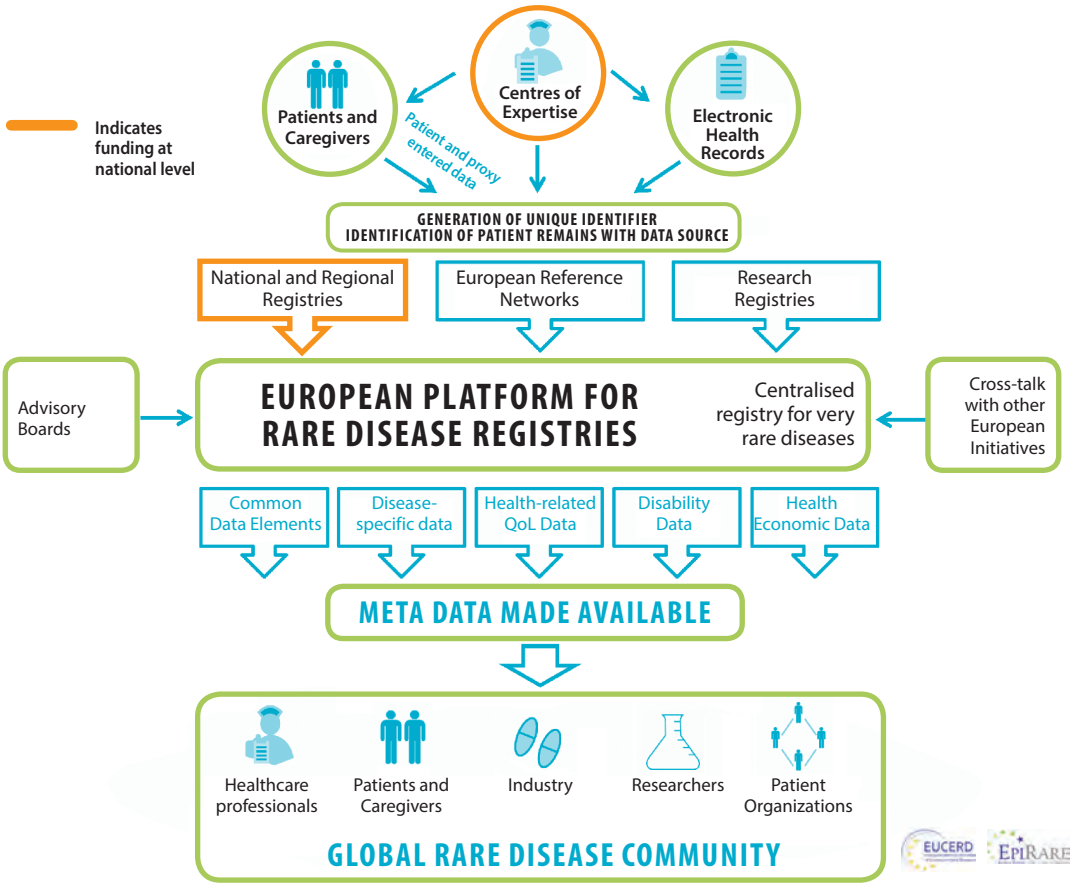
According to the policy scenario developed by EURORDIS within the EPIRARE project and discussed with both the EU Committee of Experts on Rare Diseases (EUCERD) and the JRC, the eventual governance structure of the Platform shall be comprised of one Executive Board and supporting governing bodies (e.g. Executive Committee and JRC-IHCP, Scientific/ Technological Advisory Board, Ethics Review Board, Data Request Oversight Board, Patient Advocates Working Group, Healthcare/Social Services Providers Working Group, Industry Working Group). Regular meetings and terms of office must be specified for each.

Throughout the duration of the Platform's functions, the EUCERD should serve as a scientific advisor on strategic decisions in its implementation, maintenance and sustainability. The EUCERD should remain at the core of the Platform governance structure so as to integrate policies on rare disease registries within and consistently with the broader EU policy on rare disease research and public health programmes while aligning the policies and actions of the European Commission, all EU Member States and stakeholders.
The Governance principles for the Platform will be based on the state-of-the-art in adaptive policies, procedures and structures. An adaptive governance structure will respond to uncertainty through several stages of development and a series of characteristics and underlying principles, flexible and reactive in nature.

• DATA

Proposed data flow could include patient data that enters via multiple data sources into multiple registries at the regional, national and European levels. This data includes, at a minimum the Common Data Elements in addition to other disease-specific information. Upon assignment of a unique identifier, data is referenced in the Platform and eventually centralised for very rare diseases. Meta-analysis on data allows the provision of certain data and health indicators to be freely shared with rare disease community stakeholders.

A distinction will be made between data that is collected through nationally/regionally-funded efforts and data collected through European support.



A clear, transparent, documented data access process will guide the decisions of the Data Request Oversight Board and Ethics Review Board. The process will include a minimal data request and review and appropriate data use agreement for de-identified data. Identifiable data requests will be made to the original data sources via the Platform. Patients may opt-in to be directly or indirectly contacted for opportunities to participate in further studies.

• SUSTAINABILITY

To date, most rare disease patient registries have been developed on a disease-specific or product specific basis supported either by a patient group, research or health care provider network or private enterprise, each with a unique set of challenges and objectives. Taking advantage of economies of scale, the Platform will centralize efforts to overcome challenges and streamline objectives into one platform, addressing the needs of all stakeholders in the rare disease community on a longer-term basis. A specific, long-term sustainability plan should be formalised as soon as possible to foster the principle of trust required to encourage participation.

Initial funding for the Platform will reflect the European Commission project grant indicative amount of 2 M€ further specified in the Agreement with the JRC as referred to in Section 4.2.4.4 of the Commission Implementing Decision of 28 November 2012 concerning the adoption of

the 2013 work plan in the framework of the 2nd programme of Community action in the field of health (2008-2013). This initially dedicated funding will support Phase 1 of the Platform.

Continued funding of the Platform must be aligned with the Health for Growth (3rd programme of Community action in the field of health 2014-2020) and Horizon 2020 (8th Framework Programme for Research and Innovation) proposals. Several options exist:

- Renewed funding as a project grant in the Health for Growth program 2014-2020
- Support of the Platform by the Community legal framework European Research Infrastructure Consortium (ERIC)
- A combination of these options and public-private partnerships to include industry needs

Options for a funding scheme can be summarised as follows:

- European Commission to provide funding JRC-IHCP for acting as the custodian of the Platform
- European Commission to financially support registries created by European Reference Networks and European Rare Disease research networks
- Member States to financially support national rare disease patient registries, Centres of Expertise, co-fund European Reference Networks and European rare disease research projects
- Industry to financially support specific rare disease clinical research and specific regulatory registration activities
- Academic funding (from national or EC or International, public or private sources) for specific rare disease research activities

The Platform policy for financial incentives could envisage any or all of the following possibilities:

- Patient organisations to provide overall support, patient outreach and patient-reported data
- Requirement by the European Commission for European Reference Networks or European rare disease research projects to use Platform services as part of financial support policy
- Requirement by Member States for Centre of Expertise or national research projects to use the Platform services as part of a financial support policy
- Healthcare providers to get professional credits for entering the data and recognition via micro-publications
- Fee for service model for industry or other private research purposes
- Reinvestment of any fees collected to sponsor education, training and administrative support for specific patient organisations and European Reference Networks in the case of disease-specific context and umbrella rare disease patient organisations and alliances and learned societies in the context of groups of rare diseases.

THE FUTURE OF RARE DISEASE PATIENT REGISTRIES

Each of these initiatives presents an equally powerful opportunity to overcoming challenges in concerting efforts in the registration of rare disease patients in a continually changing landscape. What is important is that each initiative takes into consideration the undeniable arguments for developing globally accepted definitions, classifications and data standards as well as favourable, congruent policies and resources for rare disease patient registries that are sustainable over time.

As illustrated by the current European and international initiatives in the field, as well as by the patient experiences and expectations presented in this book, there is overlap and consensus on many aspects of patient data collection and registration. These commonalities have culminated in the "European Union Committee of Experts on Rare Diseases (EUCERD) Core Recommendations on Rare Disease Patient Registration and Data Collection to the European Commission, Member States and All Stakeholders" (Appendix 1) which take into consideration the view of all stakeholders including that of the patient community represented in great part in the EURORDIS-NORD-CORD Joint Declaration of 10 Key Principles for Rare Disease Patient Registries (Appendix 2) and the results of the EPIRARE Patient Survey. The EUCERD Registry Working Group has proposed to ensure the implementation, practicality and coherence of the various recommendations and establish processes for monitoring their impact. It has also proposed to take the role of facilitating the provision and coherence of rare disease patient registries in the Member States.

EURORDIS views the future of rare disease patient registries as an essential tool for long-term knowledge generation on each rare disease and across all rare diseases, for the optimal planning of health and social services, the timely development of treatments or continued post-approval data collection of innovative medicines and iterative improvements of treatment protocols. The primary value of this multipurpose tool relies on the high quality of the data collected – that is the most comprehensive and accurate information about people living with rare diseases. These data, ultimately belonging to patients, must be made widely accessible to all stakeholders in a respectful and sustainable framework.

As such, EURORDIS is actively supporting a publically initiated and managed EU Platform that, at its core, promotes and defends public interests. The sustainability of this Platform can be furthered by the launch of an EU Research Infrastructure for Rare Diseases that could bring together all facilities, resources and related services (including those for registries) used by the scientific community to conduct top-level research in the field of rare diseases, ranging from social sciences to genomics. Funded from a range of public and private sources, such an infrastructure will facilitate partnership of all stakeholders – including healthcare professionals, academic researchers, industry, regulators, and patient groups. It will involve patient organisations able to represent patients' and family's interests and rights in its governance and be open to global registry activities, policies and partnerships.

EURORDIS encourages its constituents to be active at any level of the establishment, governance and sustainability of rare disease patient registry activities and recognizes the importance of its mission to build the capacity of patients and patient organisations to be best empowered to act. Through capacity building workshops and the generation of education materials in the framework of, EPRIARE, RD-Connect, European Patients' Academy on Therapeutic Innovation (EUPATI), annual EURORDIS Membership Meetings, the EURORDIS-organised European Conference for Rare Disease, the EURORDIS Summer School, its website and global communication channels, EURORDIS has integrated the mission to empower the patient community on rare disease patient registries and projects this mission long into the future.

APPENDICES

APPENDIX 1

EUCERD
European Union Committee of Experts on Rare Diseases

EUCERD CORE RECOMMENDATIONS ON RARE DISEASE PATIENT REGISTRATION AND DATA COLLECTION

TO THE EUROPEAN COMMISSION, MEMBER STATES AND ALL STAKEHOLDERS

www.eucerd.eu

5 JUNE 2013

APPENDIX 2

EURORDIS-NORD-CORD
Joint Declaration of 10 Key Principles for Rare Disease Patient Registries

1. Patient Registries should be recognised as a global priority in the field of Rare Diseases.
2. Rare Disease Patient Registries should encompass the widest geographic scope possible.
3. Rare Disease Patient Registries should be centred on a disease or group of diseases rather than a therapeutic intervention.
4. Interoperability and harmonization between Rare Disease Patient Registries should be consistently pursued.
5. A minimum set of Common Data Elements should be consistently used in all Rare Disease Patient Registries.
6. Rare Disease Patient Registries data should be linked with corresponding biobank data.
7. Rare Disease Patient Registries should include data directly reported by patients along with data reported by healthcare professionals
8. Public-Private Partnerships should be encouraged to ensure sustainability of Rare Disease Patient Registries.
9. Patients should be equally involved with other stakeholders in the governance of Rare Disease Patient Registries.
10. Rare Disease Patient Registries should serve as key instruments for building and empowering patient communities.

On behalf of an estimated 60 million people living with rare diseases in Europe and North America, the European Organisation for Rare Diseases (EURORDIS), the National Organization for Rare Disorders (NORD) and the Canadian Organization for Rare Disorders (CORD), jointly submit the following declaration on common principles regarding Rare Disease Patient Registries.
EURORDIS, NORD and CORD, along with the patients they represent in Europe and in North America, recognize that Rare Disease Patient Registries constitute key instruments for increasing knowledge on rare diseases, supporting fundamental clinical and epidemiological research, and post-marketing surveillance of orphan drugs and treatments used off-label. Furthermore, and of great importance for patients and their families, they can be instrumental in supporting health and social services planning. Rare Disease Patient Registries are powerful, cost-effective instruments to improve the overall quality of care, quality of life and survival of patients.
EURORDIS, NORD and CORD also recognize that patient involvement is a key element in the successful establishment and long-term maintenance of Rare Disease Patient Registries and many patient groups are already very active and capable in this role. On behalf of rare disease patients and their representatives in Europe and in North America, we would like to jointly put forward the following common reflections and principles regarding patient registries. These common reflections and principles may serve as a reference to all other stakeholders when shaping policies and taking actions in the field of Rare Disease Patient Registries.
A Patient Registry can be defined as an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s) . The following principles refer to this definition.

1. Patient Registries should be recognised as a global priority in the field of Rare Diseases.

Rare Disease Patient Registries represent a fundamental research effort upon which a number of critical activities are based. They constitute key instruments for increasing knowledge on rare diseases, by pooling data for epidemiological research, clinical research, and real-life post-marketing observational studies .
They broadly support health and social service planning by playing a pivotal role in healthcare organization. In particular, Centres of Expertise/Excellence and the European and International networks that connect them centralize patient data patient registries which can be used as an evidence base to shape regional, national and international health policy and standards of care.
It has also been demonstrated that Patient Registries are a major determinant for successful translational research in the field rare diseases. Where well-implemented registries and active patient organizations exist, the likelihood for developing a treatment for the disease in question is increased . Furthermore, the consistent longitudinal collection of patient data facilitates the creation of standards of care and dramatically improves patient outcomes and life expectancy even in the absence of new therapies.
The compelling arguments for Rare Disease Patient Registries as indispensable infrastructure tools for translating basic and clinical research into therapeutic solutions have elevated their status to a major priority for all stakeholders - a building block of any sound rare disease policy.

2. Rare Disease Patient Registries should encompass the widest geographic scope possible.

Due to the low individual prevalence and the scarcity of information related to each rare disease, collaboration and maximum use of limited resources is particularly meaningful for rare diseases. This is especially true for very rare diseases where no single institution, and in many cases no single country, has a sufficient number of patients to conduct fundamental, clinical and translational research. In fact, geographic dispersion of patients continues to make recruitment for clinical trials difficult, often aggravated by the dearth of scientific and medical knowledge and relevant endpoints for study designs. The International Rare Diseases Research Consortium (IRDiRC) , launched in April 2011, fosters international collaboration in research on RD. Canada, Europe and the United States have fully committed to this endeavour agreeing on the principle that maximizing scarce resources and coordinating research efforts are key elements for success in the rare disease field. IRDiRC advocates that the worldwide sharing of information, data and samples gathered by robust and harmonised Rare Disease Patient Registries will boost research at all levels and ultimately favor therapy development.

3. Rare Disease Patient Registries should be centred on a disease or group of disease rather than a therapeutic intervention.

Treatment-specific registries, frequently funded by industry, are required by regulators to monitor the effectiveness and side-effects of treatments approved under exceptional circumstances. However, because treatment-specific registries must be re-created for each product, limitations in their completeness, quality, and cost-effectiveness have been demonstrated. Consensus is growing around the opinion that disease-centric patient registries provide a more comprehensive and collaborative approach to rare disease patient data collection by aligning stakeholder efforts, avoiding fragmentation of patient populations and dissipation of resources, and ultimately addressing regulatory and payer requirements with greater accuracy.

4. Interoperability and harmonization between Rare Disease Patient Registries should be consistently pursued.

Centres of Expertise/Excellence and the international networks that connect them play a pivotal role in capturing data of patients treated at their facilities and centralizing them in Rare Disease Patient Registries. Nevertheless, no uniform, accepted standards currently govern the collection, organization, or availability of data collected by Rare Disease Patient Registries which may even vary within the same

disease group or health system. Moreover, registry custodians frequently hold proprietary views on their data or face legal limitations on data-sharing as a result of patient consent restrictions and privacy protection or conflicting national legislations. These data-sharing barriers create a compelling argument for developing globally accepted definitions, classifications, ontologies , , data standards and favourable and congruent policies and resources facilitating data sharing and pooling. Ideally, standard operating procedures and common resources or platforms for centralizing new or existing registries should be developed.

5. A minimum set of Common Data Elements should be consistently used in all Rare Disease Patient Registries.

A pillar for the systematic, coordinated approach to Rare Disease Patient Registries would be the definition of minimum set of Common Data Elements (CDEs) and corresponding validated standards and ontologies globally endorsed by all stakeholders. The consistent use of CDEs would facilitate the standardization of data (ensuring that data are defined and entered in the same way, use the same standards, and the same vocabularies), harmonization (allowing data to be more easily exchanged and compared), and interoperability (enabling common strategies for quality assurance and data security). Lastly, the definition of CDEs will allow greater opportunities for meta-analysis across diseases providing evidence for public health and social planning. The NIH Office of Rare Disease Research and EPIRARE are currently establishing such CDEs for North America and Europe.

6. Rare Disease Patient Registries data should be linked with corresponding biobank data.

Biobanks are collections of human biomaterials and represent an essential tool for fundamental and translational research. The high value of biological samples only increases when coupled with well-documented, associated data housed in a patient registry. The development of a system that assigns a unique global identifier to each patient is recommended to facilitate data linkage and avoid duplicate entries and waste of precious biomaterial. Engagement of patients and patient organizations is instrumental for the development of networks between registries and biobanks.

7. Rare Disease Patient Registries should include data directly reported by patients along with data reported by healthcare professionals.

Many patient organizations in Europe and North America are actively and successfully collecting clinical and non-clinical patient data. Most stakeholders in the rare disease community recognized that patients and their caregivers are best placed to report on their health-related quality of life, satisfaction with and utility of care and treatment. Much progress has been made in creating regulatory standards, to validate this type of data reported by patients and caregivers, which are also of significant benefit to patients' management of their own outcomes.
Out of necessity, patient groups further proceeded to collect data beyond perceived outcomes and collect post-marketing treatment outcomes, off-label drug use outcomes and even natural history data.
By complementing clinician-reported data in Rare Disease Patient Registries, patients can contribute to improving their robustness, comprehensiveness and quality. Continued creation of easily accessible and validated standards, platforms and scientific guidance to ensure the high quality collection of patient entered clinical data should be encouraged and guaranteed.

8. Public-private partnerships should be encouraged to ensure sustainability of Rare Disease Patient Registries.

In context of the current economic climate, the need for the optimal sharing of resources is an imperative. Different scenarios are being proposed to provide financial sustainability to registries and their networks, and the most promising rely on the collaboration amongst all the stakeholders .
This collaborative approach has been recognized as a requirement to: avoid duplication of efforts and

take advantage of economies of scale; foster improved quality and robustness of data collected; to unify patient data especially for diseases where several treatments exist, and best sustain registries as long-term endeavours. With both governments and private groups showing interest in patient registries, public-private partnerships are a promising collaborative scheme. Patient groups can be instrumental facilitators of public-private partnerships driving the common goals of all stakeholders through a patient-centred approach and assuring optimal efficiency and transparency. Regulatory bodies can strongly encourage such collaboration in this pre-competitive space. The nature of potential public-private partnerships, the issues to consider when establishing such a partnership, and best practices enhancing the success of such efforts should be investigated in a prompt and transparent manner.

9. Patients should be equally involved with other stakeholders in the governance of Rare Disease Patient Registries.

Patient involvement is a key element in the successful establishment of registries and many patient groups are already very active in this role. Patients should be involved at all levels of development, management and maintenance in order to best represent patient needs, increase awareness among all stakeholders of the existence of the registry and, ultimately, improving the quality and quantity of data collected through a patient-centred approach. Patient groups are willing and able to be involved in initiating the establishment of registries; defining content and purposes of the registries; resolving ethical and legal issues; authorising access and utilisation of data; creating partnerships with health professionals and industry representatives; contributing to the selection of data items collected (in particular on the impact of the disease on their daily life); helping to recruit patients for participation into the registry; preparing specific information for patients to be registered prior to their consent; motivating health professionals to input data, and directly entering data. This essential role of the patients should be reflected in the governance of the registry.

10. Rare Disease Patient Registries should serve as key instruments to build and empower patient communities.

Registries can be instrumental in building patient communities around a disease, a cluster of diseases or even common clinical features or common underlying causes. Registries thus become the aggregation point around which an organised patient community can be built where none exists. The creation of a patient registry can facilitate the congregation of patients and their families as they engage directly into the development of the very databases in which their data will be entered. Registries thus become the medical home for patients scattered internationally and empower patients with data available to share with health care professionals, clinical researchers and drug developers.

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The publication of *The Voice of Rare Disease Patients* comes at a moment when the European landscape on rare disease patient registries is undergoing a profound and progressive convergence of efforts. While registries have historically been regarded as epidemiological tools, they are now recongnised by the rare disease community as instrumental in capturing unmet public health needs and advancing research. This new wave of interest and participation is leading to a significant breach in longstanding barriers that have hindered effective collection and sharing of data. With its publication alongside the European Commission's strategic objective to implement a European Platform for Rare Disease Registration, this book proposes public health and policy solutions to accomplish this task.

The Voice of Rare Disease Patients also represents a new era in rare disease patient registries, where patients and patient organizations are active participants and partners. In this book, patients have contributed an unprecedented amount of collective information about their expectations. The patient voice is now able to drive innovation in patient registration and data collection solutions that, at their core, reflect the expectations of the European rare disease patient community.

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